EXHIBIT A

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

In re: Valsartan, Losartan, and Irbesartan Products Liability Litigation

MDL No. 1:19-md-2875

Expert Report of Herman J. Gibb, Ph.D., M.P.H.

Gibb Epidemiology Consulting LLC

Introduction

I am retained by counsel for the Defendants to provide my expert opinion as to whether use of Valsartan is associated with an increased risk of cancer.[1] I reserve the right to supplement the report should additional information become available. The following report is provided pursuant to Rule 26 of the Federal Rules of Civil Procedure. All the opinions that I have offered in this report are given to a reasonable degree of scientific certainty. My opinions are based on my education, training, knowledge, experience and/or materials that I have reviewed in connection with this litigation, which are substantial. This has allowed me to perform a complete analysis of each Plaintiffs' allegations related to Valsartan. This report is not meant to be an exhaustive recitation of all my opinions in the above-referenced cases.

My curriculum vitae, which details my education and experience, and includes a list of all publications authored by me in the past 10 years, is attached to this report as Exhibit A. A list of the materials upon which I have considered is attached to this report as Exhibit B. Citations to specific reference material also are offered in this report, where I believe it necessary to cite a specific source; otherwise, my opinions are derived from a combination of reference sources, my own professional experience, and general professional knowledge. I reserve the right to supplement this list, as well as to amend and supplement the opinions expressed in this report. I also reserve the right to respond to and rebut all information provided in discovery, which I understand is ongoing, and any opinions offered by Plaintiffs' experts at their depositions or at trial. My fees charged in connection with this engagement are consistent with my normal practice for such work. My fee schedule is attached as Exhibit C. My list of prior testimony during the previous four years is attached as Exhibit D.

Qualifications

I am President of Gibb Epidemiology Consulting LLC in Arlington, VA. I have a Ph.D. in Epidemiology (Johns Hopkins University School of Hygiene and Public Health, 1989) and an M.P.H. in Environmental Health (University of Pittsburgh Graduate School of Public Health, 1974). I chaired the Chemical and Toxins Task Force of the World Health Organization's Foodborne Epidemiology Reference Group (2007-2015). I was a member of the Science Advisory Committee of the United States Transuranium and Uranium Registries at Washington State University (2007-2016), a member of the Presidential Advisory Board on Science, Technology, Engineering, Mathematics and Health at the Ana G. Mendez University System in San Juan, Puerto Rico (2001-2016), and a member of the Pool of Scientific Advisors of the European Commission (EC) appointed by the EC's Health and Consumers Directorate-General (2009-2014). I served as Secretary-Treasurer of the Ethical, Legal, Forensics, and Societal Issues Specialty Section of the Society of Toxicology (2018-2020). I have served on several committees of the National Academies of Science, Engineering and Medicine. I am a Professorial Lecturer in Environmental and Occupational Health at the George Washington University Milken Institute School of Public Health. Prior to starting Gibb Epidemiology Consulting in April 2014, I was President of Tetra Tech Sciences, an operating unit of the Tetra Tech Corporation specializing in

[1] This report contains my opinions regarding general causation only, as requested by counsel. This report is not intended to be an exhaustive recitation of all my opinions in this litigation, and I expressly reserve the right to amend or supplement this report to offer additional opinions, including opinions on liability, specific causation, damages, or other defenses, at the appropriate stage of litigation.

health risk assessment. Prior to joining Tetra Tech Sciences in January 2004, I held several positions at the National Center for Environmental Assessment at the U.S. Environmental Protection Agency including Associate Director for Health, Assistant Center Director, and staff epidemiologist. While at EPA, I provided consultation to several foreign governments and served on a number of Task Groups and Review Boards of the International Program on Chemical Safety (IPCS). I am the author or co-author of numerous publications on epidemiology and health risk assessment. I have been the speaker, including the keynote speaker, at various international symposia on health risk assessment. I was co-author of the International Program on Chemical Safety's Environmental Health Criteria Document, *Principles for the Assessment of Risks to Human Health from Exposure to Chemicals*. I received EPA's Scientific and Technological Award as the senior author of an epidemiologic study on chromate production workers, EPA's Gold Medal for Exceptional Service for my analysis of the epidemiologic studies on arsenic, and EPA's Award for September 11 Activities, World Trade Center Particulate Matter Toxicological Assessment Team. In 2011, I received the Practitioner of the Year Award from the Society for Risk Analysis. In 2019, I received the University of Pittsburgh Public Health Distinguished Alumni Award in recognition of "contributions to environmental and occupational risk assessment."

Opinions

I have been retained by counsel for Defendants to answer the following questions:

1. Where there is reliable scientific basis to establish N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) as human carcinogens; and
2. Whether consuming recalled valsartan or valsartan containing drugs with trace amounts of NDMA or NDEA increases the risk of cancer.

After performing an extensive literature search, examining several relevant scientific articles and documents produced in this litigation, and conducting thorough analysis of the risk factors associated with the numerous cancer types alleged by Plaintiffs in this litigation, I provide the following list of opinions based on a reasonable degree of scientific certainty:

1. There is no reliable basis to establish NDMA and NDEA as human carcinogens.

2. Consuming valsartan and valsartan-containing drugs with levels of NDMA and NDEA at issue in this litigation does not increase the risk of cancer.

3. Valsartan and valsartan-containing drugs with levels of NDMA and NDEA at issue in this litigation are not unreasonably dangerous.

4. Dietary studies of NDMA and NDEA and cancer fail to support a causal association.

5. Occupational studies of rubber workers should not be utilized to examine the association between consumption of valsartan with NDMA and NDEA impurity and cancer.

Background

Claims by the plaintiffs in this case allege that NDMA and NDEA impurities in valsartan increase the risk of cancer. This report will describe how the general population is exposed to NDMA and NDEA; the epidemiologic studies of valsartan and ranitidine with NDMA

impurities; epidemiologic studies of other sources, specifically the diet, of NDMA and NDEA; and acceptable intakes of NDMA and NDEA. The report will focus specifically on the cancer types alleged by the plaintiffs: bladder, blood and bone marrow, breast, colorectal, esophageal, gastric/stomach, kidney, liver, lung, pancreatic, pharyngeal, prostate, and uterine. The report will evaluate the epidemiologic data for NDMA and NDEA and various types of cancer using Bradford Hill criteria. Finally, the report will address the claims made by experts for the plaintiffs.

General Population Exposure to NDMA and NDEA

General

According to the Agency for Toxic Substances and Disease Registry (ATSDR) of the Centers for Disease Control and Prevention (CDC) indicates that "the general population may be exposed to NDMA from a wide variety of sources, including environmental, consumer, and occupational sources." The main sources of exposure to NDMA are from tobacco smoke, chewing tobacco, diet (cured meats, beer, fish, cheese, etc.), personal care products such as shampoos and cleansers, interior air of cars, and other household items including detergents and pesticides (ATSDR 2014). NDEA has been detected in various food items and beverages and in tobacco smoke (Park et al. 2015; Walker et al. 1979; Talhout et al. 2011). Both NDMA and NDEA have been detected in drinking water (WHO 2008; Hrudey et al. 2013). In food, nitrosamines, including NDMA and NDEA, are formed by reactions of nitrogen oxide with amines (Park et al. 2015).

Both NDMA and NDEA are produced in the human body (i.e., endogenously") by acid-catalyzed nitrosation and biologically-catalyzed nitrosation, including systemic nitrosation (Hrudey et al. 2013; ATSDR 2014). Regarding endogenous production of these nitrosamines, Hrudey et al. (2013) state that "NDEA would be expected to be more dependent upon exogenous precursors than is formation of NDMA."

The World Health Organization (WHO) provided a "worst-case estimation" of daily NDMA intake of 0.005-0.016 µg/kg[2] per day based on exposure from contaminated air, water, and food (WHO 2008).

NDMA in the Diet

NDMA is present in food and can be formed during food processing, preservation and/or preparation from precursor compounds already present in, or added to, the specific food items (WHO 2008). Foods that most commonly contain NDMA include: 1) food preserved by the addition of nitrate and/or nitrite, such as cured meat products like bacon and cheeses; 2) foods preserved by smoking; 3) foods dried by combustion gases such as malt, low-fat dried milk products, and spices; 4) pickled and salt-preserved foods, particularly pickled vegetables; 5) foods grown or stored under humid conditions (WHO 2008).

A few studies have examined NDMA concentrations in foods and beverages (Biaudet et al. 1994; Tricker et al. 1991a; Park et al. 2015). Biaudet et al. (1994) measured the content of NDMA in 556 food samples and 75 beverages purchased in France over the 1987 to 1992 time period. The authors estimated that the mean daily intake was 0.19 µg/day, one-third of which was attributed to consumption of alcoholic beverages (Biaudet et al. 1994). Biaudet and

[2] Of body weight based on a 20 to 59-year old (WHO 2008). Assuming the average person weighs 70 kg, these values are equivalent to 0.35 µg/day and 1.12 µg/day, respectively.

colleagues state that "NDMA is the most commonly encountered volatile nitrosamine in food samples and the one present in the largest amounts." Tricker et al. (1991a) measured NDMA in 38 alcoholic drinks and 215 food samples in West Germany and reported that the average daily intake of NDMA was 0.28 µg/day. Tricker et al (1991a) reported that, among men, 31% of daily NDMA exposure resulted from the consumption of beer. Park et al. (2015) conducted an analysis of N-nitrosamines including NDMA and NDEA, in various food items in South Korea. The authors indicate that the concentration of NDMA was the highest in seasoning and appeared most frequently in livestock and fishery food products (Park et al. 2015).

Two studies conducted in the United States, Fristachi and Rice (2007) and Hrudey et al. (2013), estimated NDMA intake from food and beverages. Fristachi and Rice (2007) used Biaudet et al. (1994) and Tricker et al. (1991a) as the sources for NDMA measurement in various foods. Fristachi and Rice (2007) estimated daily NDMA intake to be 0.11 µg/kg from exogenous sources. Hrudey and colleagues utilized data from Biaudet et al. (1994) to estimate average NDMA intake from the diet. Hrudey et al. (2013) state that they estimated daily dietary intake of NDMA in the U.S. population to range from 0.03 to 0.06 µg/day, with adults aged 20 to 49 years having an average of 0.06 µg/day or 0.08 µg/day when beer was included in the estimate. Hrudey et al. (2013) states that "Beer consumption makes a strong contribution to NDMA intake and in our model beer consumption at the average *per capita* rate increases the dietary NDMA intake by approximately 33% in adults aged 20-49 years."

NDEA in the Diet

In comparison to NDMA, less is published on dietary intake of NDEA. Park et al. (2015) provides concentrations of NDEA in various food items. For example, Park et al. (2015) report NDEA contents in cereals and potato (not detected [ND]-0.72 µg/kg), flours (ND-0.66 µg/kg), fresh (ND-1.53 µg/kg) and frozen (3.9 µg/kg) vegetables, fruits (ND-0.60 µg/kg), breads including croquettes and doughnuts (ND-0.91 µg/kg), snacks (ND-2.22 µg/kg), salted fish (7.65-50.27 µg/kg), smoked pork brisket (0.06-9.5 µg/kg), various smoked sausages (0.91-10.3 µg/kg). NDEA was also found in varying degrees in beer and malt beverages (Park et al. 2015). Park and colleagues indicate that NDEA had the highest detection rate in agricultural foods. Walker et al. (1979) state that traces of NDEA were detected in spirits and ciders.

NDMA and NDEA in Drinking Water

NDMA and NDEA have also been detected in drinking water (WHO 2008; Hrudey et al. 2013). Hrudey et al. (2013) provide results of data from EPA's Unregulated Contaminated Monitoring Rule (UCMR) 2 data. NDEA and NDMA were detected in 0.26% and 10.2% of over 18,000 drinking water samples, respectively (Hrudey et al. 2013). The maximum concentrations of NDEA and NDMA that were measured were 100 and 630 ng/L, respectively (Hrudey et al. 2013). WHO (2008) indicates that the daily intake of NDMA from ingestion of drinking water is estimated at 0.0003-0.001 µg/kg of body weight per day.

NDMA and NDEA from Cigarette Smoke

Tricker et al. (1991b) reported that NDMA concentrations in cigarettes range from 6.3 to 76.4 ng/cigarette. WHO (2008) indicates that in homes "not containing environmental tobacco smoke, the major source of exposure to NDMA is food (0.0043-0.011 µg/kg of body weight per day)." In homes where there is regular indoor exposure to environmental tobacco smoke, however, "this source [environmental tobacco smoke] would exceed all the other sources combined by almost an order of magnitude (0.05 µg/kg of body weight per day)" (WHO 2008). Tricker et al. (1991b) report that they have "never detected NDEA in mainstream tobacco

smoke." Talhout et al. (2011), however, includes NDEA as a hazardous component of tobacco smoke.

Valsartan

On July 13, 2018, the United States Food and Drug Administration (FDA) issued a news release to alert health care professionals and patients of a voluntary recall of drug products containing the active pharmaceutical ingredient (API) valsartan due to the presence of an impurity, NDMA (FDA 2018a). Valsartan is an angiotensin II receptor blockers (ARBs) that is intended to treat high blood pressure and heart failure (FDA 2019a). Valsartan-containing products produced by several companies were included in the recall (FDA 2018a). The active pharmaceutical ingredient ("API") for the valsartan at issue was supplied to these companies by Zhejiang Huahai Pharmaceuticals (ZHP) in Linhai, China (FDA 2018a).

A July 27, 2018 FDA press release indicates that consuming up to 0.096 µg NDMA/day is considered reasonably safe for human ingestion (FDA 2018b). The press release also indicates that patients taking valsartan from a recalled batch should continue to take their current medication until their doctor or pharmacist provides a replacement or different treatment option (FDA 2018b).

On September 13, 2018, the FDA issued a press release indicating that an additional impurity, NDEA, was detected in valsartan drug products (FDA 2018c). It states, "The FDA and the European Medicines Agency have learned that Zhejiang Huahai Pharmaceuticals (ZHP) found NDEA in several batches of its valsartan API." However, according to FDA testing, not all products using ZHP valsartan API contain NDEA (FDA 2018c). In addition, NDEA was also detected in valsartan API manufactured by Mylan Laboratories, Ltd. ("Mylan").

The FDA estimated that if 8,000 people took the highest valsartan dose of 320 mg containing NDMA daily for four years, there may be one additional case of cancer over the lifetimes of the 8,000 people (FDA 2018b; FDA 2019a). For NDEA, the FDA estimated that if 18,000 people took the same dose of valsartan containing NDEA for four years, there may be one additional case of cancer over the lifetimes of the 18,000 people (FDA 2019a).

The values of NDMA and NDEA in the valsartan products as reported by the FDA can be found in Table 1, below (FDA 2019a).

Table 1. FDA's testing of NDMA and NDEA levels in valsartan products

Company	Product (tablets)	Lots Tested	NDMA level (micrograms - mcg/tablet)	NDEA level (micrograms - mcg/tablet)
Aurobindo Pharma Ltd	Amlodipine 10mg/Valsartan 320 mg	VKSA18005-A, VKSA18007-A, VKSA18001-A	Below LOD[3]	0.02-0.09
Aurobindo Pharma Ltd	Valsartan 320mg	VUSD17008-A, VUSD17001-A, VUSD17009-A	Below LOD	0-0.05

[3] According to a separate report, the limit of detection (LOD) for FDA's testing method of NDMA in valsartan was 0.005 ppm; the LOD for NDEA was 0.02 ppm (FDA 2019b).

Aurobindo Pharma Ltd	Valsartan 320mg/HCT 25mg	HTSB18001-A, HTSB18028-A, HTSB18029-A	Below LOD	0.02-0.19
Hetero Labs Ltd	Valsartan 320mg	VLS18049, VLS18051, VLS18050	0.33-0.44	Below LOD
Mylan Pharmaceutical Inc.	Amlodipine 10mg/Valsartan 320 mg	3079709, 3077618, 3079708	Below LOD	0.04-0.11
Mylan Pharmaceutical Inc.	Amlodipine 10mg/Valsartan 320 mg/HCT 25mg	2008702	Below LOD	0.05
Mylan Pharmaceutical Inc.	Valsartan 320mg	3080009, 3080010, 3079205	Below LOD	0.07-0.16
Mylan Pharmaceutical Inc.	Valsartan 320mg/HCT 25mg	3084886, 3093804, 3084862	Below LOD	0.20-0.38
Prinston Pharmaceutical	Valsartan 320mg	344B18027, 344B18028, 344B18029	15.18-16.30	Below LOD
Prinston Pharmaceutical	Valsartan 320mg/HCTZ 25mg	611B18025, 611B18026, 611B18027	13.18-20.19	Below LOD
Teva Pharmaceutical	Amlodipine 10mg/Valsartan 320 mg	26X053, 26X054, 26X055, 26X051, 26X044, 26X048	Below LOD	0-0.03
Teva Pharmaceutical	Amlodipine 10mg/Valsartan 320 mg/HCT 25mg	22X045, 22X046, 22X047, 22X038, 22X041	Below LOD	0-0.03
Teva Pharmaceuticals	Valsartan 320mg	1240425A, 1247282M	7.92-16.55	Below LOD
Teva Pharmaceuticals	Valsartan 320mg/HCTZ 25mg	1217576M, 1217577M, 1217578M	6.94-10.35	0-0.77
Torrent Pharmaceuticals	Amlodipine 10mg/Valsartan 320 mg/HCTZ 25mg	BBX2E001, BBX2E002, BBX2E003	10.24-11.53	Below LOD
Torrent Pharmaceuticals	Valsartan 320mg	BV48D001, BV48D002	0.56-0.62	1.12-1.22
Torrent Pharmaceuticals	Valsartan 160mg	BV47D001	0.45	1.31

To get an idea of the average NDMA and NDEA impurities across products, the midrange[4] values of NDMA and NDEA were calculated for each product and then averaged to get 3.86 and 0.21 micrograms per tablet,[5] respectively.

Epidemiology

Primer on Epidemiology

Epidemiology is the study of the distribution and cause of disease. There are three major observational study designs in epidemiology: cohort, case-control, and cross-sectional. In a cohort study, the investigator starts with a group of individuals apparently free of the disease of interest. This group of individuals, or cohort, is followed through time to determine the incidence rate (or mortality rate) among the exposed and the incidence (or mortality rate) among the unexposed (Kelsey et al. 1986). In a case-control study, cases are selected based on having a certain disease or outcome; controls, on the other hand, are free of the disease or outcome (Rothman et al. 2008; Stephenson & Babiker 2000). Cross-sectional studies examine a representative sample of the source population where exposure and disease status are determined simultaneously (Rothman et al. 2008). Of the three observational epidemiologic study designs, described above, cohort studies provide the strongest evidence when examining causation (Stephenson & Babiker 2000).

Measures of association are used in epidemiology to quantify the association between exposure and disease (CDC 2012). Some of the measures of association discussed in this report include relative risk (RR), odds ratio (OR), and hazard ratio (HR). The RR compares the risk of a health event or disease among one group with the risk among another group; typically the exposed vs. the unexposed (CDC 2012). ORs are typically reported in case-control studies and describe the odds of exposure in the cases compared to the controls. Finally, a HR is a measure of how often a particular event or disease occurs in one group compared to how often it happens in another group, over time. RRs and HRs are typically reported in cohort studies (NCI Undated a). A 95% confidence interval (CI) around a measure of association can be interpreted as the range of values that are consistent with the data from a study. A 95% CI is significant if it does not contain the number 1 (CDC 2012). CDC (2012) defines a *p* value as "the probability of observing an association between two variables or a difference between two or more groups as large or larger than that observed, if the null hypothesis were true." *P*-values greater than 0.05 are typically deemed non-significant.

Literature Search Methodology

A literature search was conducted in PubMed[6] to identify the relevant literature on NDMA and NDEA exposure and various cancers. Search terms included the type of cancer (and simply the term "cancer") and NDMA or NDEA. These search terms were searched in the title and abstract fields using PubMed's Advanced Search Builder tool. Titles and abstracts of the returned studies were reviewed for relevancy; epidemiology studies that were deemed relevant

[4] Midrange=(maximum – minimum) / 2
[5] For test results that were below the LOD, the LOD was converted from ppm to micrograms per gram and then multiplied by the weight of the valsartan product to produce the LOD in micrograms. This value was then halved to assume the average test results below the LOD were approximately half of the LOD.
[6] https://pubmed.ncbi.nlm.nih.gov/

were obtained and reviewed in full. Studies in languages other than English were not included in this review.

Epidemiologic Studies of Pharmaceuticals with NDMA Impurity and Cancer

A few studies have examined the risk of cancer from pharmaceuticals with an NDMA impurity (Gomm et al. 2021; Pottegård et al. 2018; Yoon et al. 2021; Kantor et al. 2021). Gomm et al. (2021) and Pottegård et al. (2018) examined valsartan with NDMA impurity while Yoon et al. (2021), Kantor et al. (2021), and Kim et al. (2021) studied ranitidine with NDMA impurity.

Studies of valsartan

The most recent study, Gomm et al. (2021), is a large, longitudinal cohort study conducted in Germany that examined the risk of cancer from Valsartan with NDMA impurity. Data was collected from a German health insurance provider on nearly 781,000 patients who had filled a prescription for valsartan during 2012 to 2017. No association was found between exposure to valsartan with NDMA impurity and overall cancer (aHR=1.00; 95% CI 0.98-1.02). The hazard ratio was adjusted for sex; age; polypharmacy (5 or more drugs); prescription of low-dose acetylsalicyclic acid (ASA), non-ASA non-steroidal anti-inflammatory drugs, 5α-reductase inhibitors, statins, spironolactone, glucocorticoids for systemic use, selective serotonin reuptake inhibitors, and hormone replacement therapy; comorbidities including diabetes, chronic obstructive pulmonary disease (COPD), congestive heart failure, and alcohol-related diseases; the Charlson comorbidity index (CCI); and prevalent valsartan use. Gomm et al. conclude that "Causality cannot be inferred." Findings for all cancer types reported by Gomm et al. (2021) can be found in Table 2, below.

Pottegård et al. (2018) utilized Danish health registry data in Denmark to conduct a nationwide cohort study on use of valsartan products with NDMA impurity and cancer risk. This study included 5,150 Danish patients with no history of cancer, age 40 and older, that used valsartan on January 1, 2012 or started use between January 1, 2012 and June 30, 2017. Prevalent users of valsartan were defined as individuals that filled a valsartan prescription from September to the end of December 2011 and entered the study cohort on January 1, 2012. Incident users entered the cohort on the day of filling their first valsartan prescription during the study period. Participants were followed from one year after cohort entry to account for a one-year lag and followed to cancer outcome, death, migration or the end of the study period on June 30, 2018. Over 3,600 unexposed participants contributed 7,344 person-years and had 104 cancer outcomes; 3,450 participants classified as ever exposed to NDMA contributed 11,920 person-years and had 198 cancer outcomes. The adjusted hazard ratio for ever exposure and overall cancer was non-significant (aHR=1.09, 95% CI 0.85-1.41). There was also no evidence of a dose-response relationship (p=0.70) by cumulative exposure: <20,000 mg (HR=1.15, 95% CI 0.83-1.59); 20,000-49,999 mg (HR=0.99, 95% CI 0.69-1.43); ≥50,000 (HR=1.11, 95% CI 0.82-1.50). The hazard ratios were adjusted for sex, age, use of low dose aspirin, non-aspirin non-steroidal anti-inflammatory drugs, 5 α-reductase inhibitors, statins, spironolactone, oral steroids, hormone replacement therapy, selective serotonin reuptake inhibitors, history of diabetes, COPD, heart failure, alcohol related disease, Charlson comorbidity index score, and being a prevalent valsartan user. Findings for all cancer types reported by Pottegård et al. (2018) are located in Table 2.

Studies of ranitidine

Yoon and colleagues studied the risk of cancer from taking ranitidine products with NDMA impurity in a cohort of South Koreans (Yoon et al. 2021). The exposed population consisted of over 40,000 ranitidine users (prescribed between January 2009 and December 2011) for more than one year. The non-exposed population comprised over 10,000 famotidine (another H2-receptor antagonist in which no NDMA has been detected) users for more than one year (same time period as for ranitidine). Participants under age 30 were excluded. The cohort was 4:1 matched on sex, age, diabetes mellitus, and duration of drug use (cumulative exposure). Cancer outcomes (lung, liver, kidney, biliary tract, testis, stomach, colorectal, thyroid, breast, uterus, and bladder) were ascertained between January 2012 and December 2018. Data on medication use and cancer outcomes was obtained from the Health Insurance Review and Assessment (HIRA) database. The authors found no difference in the overall cancer risk between the ranitidine and famotidine groups (hazard ratio, HR=0.99 [95% CI 0.91-1.07]). The results of Yoon et al. (2021) for all cancer types are provided in Table 2.

Kantor and colleagues (2021) utilized the UK Biobank, a prospective cohort of men and women in the United Kingdom (UK), to assess whether ranitidine use was associated with an increased risk of cancer. The study was motivated by the FDA recall of ranitidine products due to potential exposure to NDMA. Cohort members completed a detailed questionnaire at baseline (2006-2010) and were followed up until October 31, 2015. Data on regular ranitidine and omeprazole use was obtained from the baseline questionnaire. Of the 459,204 participants in the study, 26,230 were diagnosed with cancer (median follow-up time was 6.7 years). The authors did not find an association between regular use of ranitidine and overall cancer risk (aHR=1.01; 95% CI 0.93-1.09); the results were similar for ranitidine use compared to the active comparator, omeprazole (aHR=0.94; 95% CI 0.85-1.04). The hazard ratios were adjusted for age, sex, race, household income, BMI, history of smoking status, pack-years, alcohol intake, physical activity, and diabetes. Full results by cancer type can be found in Table 2, below.

Kim et al. (2021) conducted a study to examine if patients taking ranitidine had a higher risk of developing digestive tract cancers compared to patients taking other acid reflux medications. The authors utilized a nationwide database, IBM Explorys, to identify three cohorts: individuals prescribed ranitidine (n=581,028); famotidine (n=909.970); and omeprazole (n=2,179,048). Yearly incidence data for esophageal, gastric, hepatocellular, pancreatic, and colorectal cancer was determined for the period 2009-2018. First-time cancer diagnoses were not included until a minimum of 1 year after initiation of the anti-reflux medication had been reached. Odds ratios were adjusted accounting for three common risk factors for each type of cancer studied. Esophageal cancer analyses were adjusted for tobacco use, alcohol use, and obesity. Gastric cancer analyses were adjusted for atrophic gastritis, tobacco use, and obesity. Pancreatic cancer analyses were adjusted for tobacco use, diabetes mellitus, and obesity. For liver cancer, the authors adjusted for cirrhosis, obesity, and chronic viral hepatitis. The analysis for colorectal cancer adjusted for obesity, diabetes mellitus and irritable bowel disease. Demographic factors adjusted for include age above or below 65, gender, race (Caucasian or African American). Odds ratios adjusting for the common cancer risk factors, described above, were calculated; these are summarized in Table 2, below. Multivariable analyses were also conducted adjusting for the demographic factors and one common cancer risk factor (see Table 4 of Kim et al. 2021). Both of these analyses examined ranitidine vs. famotidine and ranitidine vs. omeprazole, separately. None of the odds ratios were elevated for any of the gastrointestinal cancers examined.

Summary

It is clear from the epidemiologic studies of valsartan and ranitidine that there is no evidence of a causal association of either valsartan (or ranitidine) with NDMA impurity and an increased risk of cancer overall. Gomm et al. (2021) reported an increased hazard ratio for liver cancer for the entire cohort but found that long-term valsartan use was not associated with liver cancer. Kantor et al. (2021) found an increased hazard ratio for liver cancer for regular users of ranitidine (yes vs. no) but did not find an association when comparing regular use of ranitidine to regular use of omeprazole. Yoon et al. (2021) and Kim et al. (2021) found hazard ratios/odds ratios less than 1 for liver cancer and Pottegård et al. (2018) could not obtain estimates for liver cancer as there were no liver cancer events in the exposed group. It should also be noted that Gomm et al. (2021) were unable to adjust for certain liver cancer risk factors including smoking and alcohol consumption. In Kantor et al. (2021), the association between ranitidine use and liver cancer was weakened and no longer significant when compared to omeprazole, which the authors indicate "may reflect residual confounding by indication (or another jointly related factor)."

Table 2. Risk estimates (95% CI) for overall cancer and by cancer type

	Hazard Ratio (95% CI)				
Cancer Type	*Studies of valsartan with NDMA impurity*		*Studies of ranitidine with NDMA impurity*		
	Gomm et al. 2021	Pottegård et al. 2018	Yoon et al. 2021	Kantor et al. 2021	Kim et al. 2021
Overall	1.00 (0.98-1.02)	1.09 (0.85-1.41)	0.99 (0.91-1.07)	1.01 (0.93-1.09) 0.94 (0.85-1.04)[a]	N/A
Bladder	1.02 (0.95-1.11)	0.66 (0.15-2.89)	1.41 (0.88-2.25)	1.22 (0.74-2.01) 1.30 (0.69-2.46)[a]	N/A
Blood and bone marrow	N/A	N/A	N/A	N/A	N/A
Breast	1.02 (0.96-1.08)	0.85 (0.42-1.73)	0.82 (0.55-1.21)	1.04 (0.86-1.26) 1.08 (0.86-1.35)[a]	N/A
Colorectal and intestinal	0.99 (0.94-1.05)	1.46 (0.79-2.73)	0.98 (0.78-1.23)	1.12 (0.88-1.44) 1.25 (0.92-1.69)[a]	0.46 (0.43-0.49)[b] 0.66 (0.62-0.70)[c]
Esophageal	N/A	N/A	N/A	N/A	0.51 (0.43-0.60)[b] 0.62 (0.52-0.72)[c]
Stomach/gastric	N/A	N/A	1.06 (0.86-1.31)	N/A	0.43 (0.36-0.51)[b] 0.58 (0.49-0.68)[c]
Kidney	0.96 (0.87-1.05)	1.00 (0.22-4.65)	0.78 (0.49-1.25)	0.53 (0.27-1.02) 0.39 (0.19-0.82)[a]	N/A
Liver	1.16 (1.03-1.31)	N/A	0.85 (0.69-1.05)	1.91 (1.09-3.36) 1.15 (0.58-2.26)[a]	0.39 (0.36-0.41)[b] 0.81 (0.76-0.86)[c]
Lung	0.97 (0.91-1.03)	0.94 (0.47-1.91)	0.99 (0.81-1.21)	0.96 (0.72-1.27) 0.76 (0.55-1.06)[a]	N/A
Pancreatic	0.93 (0.84-1.02)	0.71 (0.21-2.44)	N/A	N/A	0.54 (0.49-0.62)[b] 0.68 (0.60-0.76)[c]
Pharyngeal	N/A	N/A	N/A	N/A	N/A
Prostate	1.00 (0.94-1.06)	1.33 (0.68-2.62)	1.01 (0.72-1.40)	1.01 (0.82-1.23) 1.02 (0.80-1.30)[a]	N/A
Uterine	1.08 (0.96-1.21)	1.81 (0.55-5.90)	1.15 (0.58-2.28)	N/A	N/A

[a] Comparison of regular ranitidine use vs. regular omeprazole (active comparator) use
[b] Comparison of ranitidine vs. famotidine
[c] Comparison of ranitidine vs. omeprazole

Allowable Daily Intake of NDMA and NDEA

As described above, the FDA indicates that human ingestion of up to 0.096 µg NDMA/day and 0.0265 µg NDEA/day is considered reasonably safe for human ingestion based on lifetime exposure (FDA 2018b; FDA 2019a). However, other studies have described allowable daily intake, permissible daily exposure, and tolerable daily intake values that are much higher than those provided by FDA (Johnson et al. 2021; Snodin and Elder 2019; Fitzgerald and Robinson 2007). In accordance with International recommendations (ICHM7; ICHQ3C and ICHQ3D), Johnson et al. (2021) calculated permissible daily exposure (PDE) levels for both NDMA and NDEA of 6.2 and 2.2 µg/day, respectively. Using *in vivo* mutagenicity data, Johnson et al. (2021) estimated PDEs of 0.6 µg/day for NDMA and 0.04 µg/day for NDEA. Snodin and Elder (2019), using the ICH M7 less-than-lifetime approach, provide a value of 0.64 µg/day if exposure is ≤10 years and 1.28 µg/day if exposure is ≤1 year. Fitzgerald and Robinson (2007) developed a tolerable daily intake for NDMA using a modified benchmark dose method and report a range of 4.0-9.3 ng/kg/day which converts to 0.280-0.651 µg/day assuming the individual weighs 70 kg.

Epidemiologic Studies of Dietary NDMA and NDEA and Cancer

General

The following sections describe studies on dietary NDMA/NDEA and the cancer types alleged by the plaintiffs. Summaries of the epidemiologic literature examining NDMA and overall cancer as well as the respective cancer types, are provided.

Overall cancer

Loh and colleagues (2011) examined the association between dietary *N*-nitroso compounds including NDMA, and risk of cancer in a prospective study of over 23,000 men and women aged 40-79 years old (Loh et al. 2011). The baseline diets of the participants were assessed with food frequency questionnaires (FFQs) which were designed to establish the average food consumption during the prior year. NDMA and nitrite/nitrate consumption was estimated by matching the FFQ food items to items in a food database developed by Jakszyn et al. (2004). Three thousand and two hundred and sixty-eight incident cancers occurred after a mean follow-up of 11.4 years. The authors reported that dietary NDMA intake was significantly associated with an increased cancer risk in both men and women (aHR=1.14; 95% CI 1.03-1.27, p-trend=0.03) when the highest quartile was compared with the lowest quartile in age- and sex-adjusted analyses. However, this association was no longer significant after further adjustment for body mass index (BMI), cigarette smoking status, alcohol intake, energy intake, physical activity status, educational level and menopausal status in women: aHR=1.10 (95% CI 0.97-1.24); the trend was also no longer significant (p=0.22). Loh et al. (2011) found a significant interaction between plasma vitamin C concentrations and dietary NDMA on cancer incidence (p=0.006): aHR (plasma vitamin C <50 µmol/L)=1.08 (95% CI 1.00-1.16); aHR (plasma vitamin C ≥50 µmol/L)=1.01 (95% CI 0.94-1.10).

No studies were found that examined dietary NDEA intake and overall cancer.

Bladder cancer

One study, Jakszyn et al. (2011), evaluated dietary NDMA intake and bladder cancer. This study included 481,419 participants from 10 European countries (EPIC cohort). Usual diet and dietary data over the previous year were obtained through country-specific questionnaires.

The authors reported the following non-significant hazard ratios for bladder cancer for quartiles of NDMA: Q2 (1.14; 95% CI 0.91-1.42); Q3 (1.07; 95% CI 0.85-1.34); Q4 (1.12; 95% CI 0.88-1.44); the *p* for trend (0.49) was also non-significant. These hazard ratios were stratified on age at recruitment, sex, and study center, and adjusted for educational level, BMI, smoking status, lifetime intensity of smoking (number of cigarettes per day), time since quitting or duration of smoking, and total energy intake. They were not able to adjust for additional risk factors of bladder cancer such as a family history or personal history of bladder cancer (ACS 2019a; Adami et al. 2018).

Breast cancer

Only one dietary study, Loh et al. (2011), examined dietary NDMA intake and breast cancer risk; they did not find an association (aHR=1.01; 95% CI 0.84-1.20).

No studies evaluated dietary NDEA intake and breast cancer.

Colorectal cancer

Several studies examine the association between dietary intake of NDMA and colorectal cancer (Loh et al. 2011; Zhu et al. 2014; Knekt et al. 1999). Loh et al. (2011), described in detail previously, reported aHRs for dietary NDMA and colon cancer and rectum cancer of 0.99 (95% CI 0.83-1.18) and 1.46 (95% CI 1.16-1.84), respectively. Several risk factors for colorectal cancer, such as race, personal history of various diseases including inflammatory bowel disease and type 2 diabetes, were not adjusted for in their analyses.

Zhu et al. (2014) conducted a case-control study examining dietary *N*-nitroso compound consumption, including NDMA, and the risk of colorectal cancer in Canada. The study included 1,760 cases with adenocarcinoma and 2,481 population controls; a FFQ was administered to evaluate dietary intake one year prior to diagnosis. The FFQ was adapted for the Canadian population and modified further to include foods indigenous to the Newfoundland population specifically. For the Newfoundland population, dietary exposures to NDMA were calculated using an instrument described by Howe et al. (1986). This instrument utilizes an estimation algorithm that identified 31 food items/groups in the questionnaires that made the greatest individual contribution to the consumption of NOC and then linked them to the National Cancer Institute of Canada's nutrient data bank. The FFQ used in the Ontario population was slightly different and approximated intakes of NOC were determined based on a report of the United States Department of Agriculture. Cases were recruited through two colorectal cancer registries and controls were identified through random digit dialing, a list of residential phone numbers or from population-based property assessment rolls. Odds ratios were adjusted for age, sex, energy intake, BMI, cigarette smoking status, education attainment, reported colon screening procedure, NSAID use, multivitamin supplements use, folate supplement use, vegetable intake, and province of residence. The authors reported a significantly increased odds ratio (OR) of colorectal cancer for the highest quintile of NDMA intake (OR=1.42; 95% CI 1.03-1.96); the *p* for trend was 0.005. In analyses by colorectal tumor subsite, only rectal cancer was significantly elevated for any quintile (OR_{Q5}=1.61; 95% CI 1.11-2.35). Unlike Loh et al. (2011), no significant interaction was found for NDMA and vitamin C (p=0.95). Zhu et al. (2014) was possibly limited by recall bias which would result in differential exposure misclassification that could bias the odds ratio away from the null.

In a prospective cohort study in Finland, Knekt et al. (1999), looked at the association between dietary intake of nitrates, nitrites, and NDMA and gastrointestinal tract cancers

including colorectal cancer. Nearly 10,000 individuals filled out a food questionnaire during recruitment between 1966 and 1972. The cohort was followed for up to 24 years; 189 patients were diagnosed with GI cancers during this time period. The study estimated that dietary NDMA was attributed to smoked and salted fish (51.9%) and cured meats and sausages (48.1%). The mean daily NDMA intake from the diet was 0.052 µg and that from beer estimated in a sub-population, was 0.071 µg. The short-term reproducibility of the daily consumption of NDMA was estimated from dietary interviews repeated 4 to 8 months apart. The authors report a "fair" intraclass correlation coefficient (ICC) for reproducibility for NDMA of 0.53.[7] The adjusted RR for the highest quartile of dietary NDMA was the only significant risk estimate for colorectal cancer: 2.12 (95% CI 1.04-4.33); however, the *p* for trend was not significant (0.47). When examined by quartiles of fish and meat intake, a significantly elevated adjusted RR was found for the highest quartile of smoked and salted fish consumption: aRR=2.58 (95% CI 1.21-5.51). RRs were adjusted for sex, age municipality, smoking, and energy intake. Interestingly, the adjusted RR (sex, age, municipality, smoking) for "above median" use of beer and colorectal cancer was non-significant (1.39; 95% CI 0.68-2.85); the p-value for trend was non-significant (p=0.71). It is important to note the following limitation mentioned by the authors: "Although the association between nitrosamine intake and colorectal cancer observed here is plausible, it cannot be excluded that it may be due to confounding." Knekt et al. cite to another study, Dich et al. (1996), which found that intake of NDMA was associated with potential risk factors of colorectal cancer in the same study population. Knekt et al. (1999) did not adjust for certain colorectal cancer risk factors including being overweight or obese, lack of physical activity, or alcohol consumption.

No studies were identified that examined dietary NDEA intake and colorectal cancer.

Esophageal cancer

Three studies, including 2 cohort studies and 1 case-control study, examine the association between dietary NDMA and esophageal cancer (Loh et al. 2011; Keszei et al. 2013; Rogers et al. 1995). The findings of these studies are described below.

Loh et al. (2011), described previously, reported a non-significant adjusted HR of 1.13 (95% CI 0.77-1.68) for NDMA intake and esophageal cancer. The hazard ratio was adjusted for age, sex, BMI, cigarette smoking status, alcohol intake, physical activity status, educational level, and menopausal status (in women).

Keszei et al. (2013) analyzed the association between NDMA and esophageal cancer in the Netherlands Cohort Study. FFQs were used to assess diet. NDMA concentrations in food items and food groups were extracted from publications where NDMA was measured in Dutch foods in the 1970s and 1980s. For food items for which NDMA levels were not available from Dutch sources, measurements made in Western or northern Europe countries were used. When NDMA concentrations were not available for a food item, the value of the closest comparable food item was used. Keszei and colleagues reported a significantly elevated adjusted HR for esophageal squamous cell carcinoma (aHR=1.15; 95% CI 1.05-1.25) in men but a non-elevated adjusted HR for esophageal adenocarcinoma (aHR=0.98; 95% CI 0.91-1.06). Similar hazard ratios were reported for women. Hazard ratios for esophageal squamous cell carcinoma were adjusted for age, smoking status, years of cigarette smoking, number of cigarettes smoked per day, total energy intake, BMI, alcoholic beverages not including beer, vegetable intake, fruit

[7] Cicchetti (1994) indicate that ICC values between 0.40 and 0.59 are considered "fair."

intake, education level, and non-occupational physical activity. Hazard ratios for esophageal adenocarcinoma were adjusted for all of the above and for lower esophageal sphincter-relaxing medications. Several risk factors of esophageal cancer, including Barrett's esophagus and HPV infection, were not adjusted for in these analyses.

Rogers et al. (1995), examined dietary consumption of NDMA and the risk of laryngeal, esophageal and oral cancer. The authors conducted a population-based case-control study with 645 cases (n=169 laryngeal, n=125 esophageal, and n=351 oral cancer) and 458 controls. Exposure to NDMA was estimated from a FFQ, indicating the participants' usual eating habits 10 years prior to the interview. For the highest tertile of NDMA (>0.179 mg/day) compared to the lowest tertile (<0.06 mg/day), the adjusted OR for esophageal cancer was non-significant: 1.86 (95% CI 0.87-3.95); the *p* for trend was also non-significant (*p*=0.063).

No studies were identified that examined dietary intake of NDEA and esophageal cancer.

Stomach or gastric cancer

Several studies examine the association between dietary NDMA and risk of stomach or gastric cancer (Song et al. 2015; Loh et al. 2011; Knekt et al. 1999; Jakszyn et al. 2006; Larsson et al. 2006; Palli et al. 2001; Pobel et al. 1995; DeStefani et al. 1998; La Vecchia et al. 1995; González et al. 1994; Risch et al. 1985). Loh et al. (2011) and Knekt et al. (1999) have already been described in detail above. Loh et al. (2011) reported an adjusted HR of 1.13 (95% CI 1.00-1.28) for gastrointestinal cancer; there was no adjustment for *H. pylori*. Knekt and colleagues (1999) did not find an increased risk between dietary NDMA and stomach cancer (RR=0.75; 95% CI 0.37-1.51).

Song et al. (2015) conducted a meta-analysis examining the association between dietary nitrates, nitrites and nitrosamines and gastric cancer. The authors calculated separate meta risk-estimates for the cohort studies (Knekt et al. 1999; Jakszyn et al. 2006; Larsson et al. 2006; Keszei et al. 2013) and for the case-control studies (LaVecchia et al. 1995; Pobel et al. 1995; DeStefani et al. 1998; Palli et al. 2001). The meta risk estimates for the cohort studies and case-control studies were 1.09 (95% CI 0.89-1.33; I^2=18.9%) and 2.05 (95% CI 1.14-3.67; I^2=88.6%), respectively. The overall meta-risk estimate, based on random effects analysis, was 1.34 (95% CI 1.02-1.76; I^2=75.8%). The meta-risk estimate was lower for studies published in 2000 or later (mRR=1.12; 95% CI 0.95-1.31; I^2=3.6%) compared to the earlier studies published prior to 2000 (mRR=2.02; 95% CI 0.96-4.24; I^2=88.3%). Additionally, the meta-risk estimate was lower (mRR=1.30; 95% CI 0.97-1.75; I^2=76.5%) for the higher quality studies than for the lower quality studies (mRR=2.47; 95% CI 0.41-14.91; I^2=85.8%); both mRRs were non-significant. Importantly, none of the estimates included in the meta-analysis of Song et al. (2015) adjusted for *H. pylori* infection. Infection with *H. pylori* is a significant risk factor for stomach cancer (ACS 2021; Adami et al. 2018). Additionally, the I^2 values reported above for the case-control studies and the overall meta-analysis indicate a high level of heterogeneity, indicating inconsistency across studies (Higgins et al. 2003).

One study included in the Song et al. (2015) analysis, Jakszyn et al. (2006), is particularly large (N=521,457) and deserves additional attention. The authors utilized data from the European Prospective Investigation into Cancer and Nutrition (EPIC – EUROGAST) to examine the relationship between gastric cancer and dietary intake of NDMA. Jakszyn et al. (2006) did not find an association between dietary NDMA and gastric cancer (aHR=1.00; 95% CI 0.7-1.43). When analyzing the data by tertiles, no dose-response was found (*p* for trend=0.96). The analysis

by Jakszyn et al. (2006) also stands out as they evaluated infection with *H. pylori*, the most important risk factor for stomach cancer. Eighty-three percent of the individuals with gastric cancer were positive for *H. pylori* compared to 66% of individuals that did not develop gastric cancer.

González et al. (1994) conducted a case-control study in 1988 and 1989 to examine the association between diet and gastric cancer in Spain. This study was not included in the Song et al. (2015) meta-analysis and is therefore summarized here. Usual diet was estimated using a dietary history questionnaire which was administered via interview. Analyses examining nitrosamines that were adjusted for total calories did not find significant trends for intestinal or diffuse gastric cancer (*p* for trend=0.101 and *p* for trend=0.133, respectively). The authors report that their findings regarding the relationship between NDMA, vitamin C, and gastric cancer as "simply suggestive of a possible biologic interaction."

There were no studies that evaluated the association between dietary intake of NDEA specifically and stomach or gastric cancer.

Lung cancer

Three studies (Loh et al. 2011; Goodman et al. 1992; DeStefani et al. 1996) examine the association between dietary intake of NDMA and lung cancer; they are described in detail, below.

Loh and colleagues reported a non-significant adjusted hazard ratio for lung cancer and dietary intake of NDMA (aHR=1.05; 95% CI 0.88-1.24). This hazard ratio was adjusted for age, sex, BMI, cigarette smoking status, alcohol intake, energy intake, physical activity status, educational level, and menopausal status (in women).

Goodman et al. (1992) carried out a population-based case-control study on Oahu, HI, of the association between dietary cholesterol and fat with lung cancer. A diet history examining 130 food items and three serving sizes was used to assess NDMA; the reference period was the year prior to diagnosis or the onset of symptoms for the cases. Goodman and colleagues vaguely describe how NDMA intake was calculated: "The consumption of nutrients was calculated by using food composition data compiled mainly from U.S. Department of Agriculture tables and supplemented with other publications." In some cases, the study subject had died or was too ill to participate; in these instances, the investigators obtained surrogate interviews from the spouse or next-of-kin. Importantly, surrogate interviews were taken for a much larger percentage of cases (29%) than for controls (7%); these differences could result in proxy response bias. Additionally, reasons for non-participation varied across potential cases and controls: 18% of potential cases did not participate due to lack of a suitable surrogate whereas only 3% of potential controls did not participate for the same reason. Significant trends were reported with increasing quartile of NDMA for both men (p=0.0006) and women (p=0.04). Among men, significant adjusted ORs were reported for Q3 (aOR=2.8; 95% CI 1.4-5.3) and Q4 (aOR=3.3; 1.7-6.2). Among women, the adjusted OR for Q4 was 2.7 (95% CI 1.0-6.9). The odds ratios were adjusted for age, ethnicity, smoking status, pack-years of cigarette use, and beta-carotene intake. Other risk factors for lung cancer, such as secondhand smoke exposure and family history, were not adjusted for (ACS 2019b; Adami et al. 2018).

DeStefani et al. (1996) conducted a hospital-based case-control study in Uruguay to assess the association between dietary NDMA and lung cancer risk. Controls were excluded if they were hospitalized for diseases that are associated with using tobacco. A FFQ was used to

estimate the usual diet during the 5-years preceding illness onset. NDMA was estimated using data from five publications representing data from four countries (United Kingdom, France, Canada, and the United States). DeStefani et al. indicate that the NDMA data "included 26 of the most frequently consumed food groups, particularly those considered to be the main sources of these nitroso compounds." The five publications reporting the NDMA data were all published in the 1970s except for the publication on the French data, which was published in 1992. The authors reported adjusted ORs for NDMA-containing foods; the only significantly (borderline) elevated OR corresponded to salted meat (aOR=1.56; 95% CI 1.01-2.42). De Stefani and colleagues reported adjusted ORs for the highest quartile of NDMA intake and smoking status; oddly, the adjusted OR was higher for nonsmokers than for smokers: nonsmokers (aOR=3.42; 95% CI 0.76-15.4) and current smokers (aOR=2.95; 95% CI 1.53-5.64). The odds ratios were adjusted for age, sex, residence, urban/rural status, education, family history of lung cancer, BMI, pack-years, and total energy intake. The authors did not use a categorical variable to adjust for smoking status as they indicated "stratification by smoking status was not suggestive of residual confounding." Other risk factors for lung cancer, including secondhand smoke exposure and exposure to radon, were not adjusted for (ACS 2019b; Adami et al. 2018). Additionally, this study was conducted in Uruguay; the dietary habits from individuals in Uruguay and the United States are not comparable.

No studies were identified that examined the association between dietary NDEA intake and lung cancer.

Pancreatic cancer

A 2019 study published by Zheng and colleagues (2019) is the only study to date that analyzes dietary NDMA (and NDEA) and pancreatic cancer. Zheng et al. (2019) conducted a hospital-based case-control study and examined N-nitroso compounds and risk of pancreatic cancer. Dietary intake of NDMA and NDEA were estimated using self-administered FFQ. Zheng et al. reported a significant trend with increasing quartiles of NDEA intake ($p<0.0001$); no trend was found for NDMA ($p=0.78$). For the fourth quartile of NDEA and NDMA intake, the adjusted ORs were 2.28 (95% CI 1.71-3.04) and 1.03 (95% CI 0.78-1.37), respectively. The odds ratios were adjusted for age group, sex, race, education level, history of diabetes, smoking status and alcohol level, BMI status, and family history of pancreatic cancer. It should be noted that Zheng et al. (2019) conclude that their findings "need to be confirmed in readily available large, prospective cohort studies with consideration of sufficient time between diet assessment to disease diagnosis or symptoms and diagnosis."

Pharyngeal cancer

Knekt et al. (1999) is the only study that examines head and neck cancer, which encompasses pharyngeal cancer. Knekt et al. (1999) reported a non-significant adjusted RR of 1.37 (95% CI 0.50-3.74) for head and neck cancer for the highest quartile of NDMA intake. Interestingly, the adjusted RRs actually decreased from the second quartile to the fourth quartile: second quartile aRR=2.82 (95% CI 1.11-7.17); third quartile aRR=1.95 (95% CI 0.73-5.17); fourth quartile aRR=1.37 (95% CI 0.50-3.74). The *p* for trend was 0.43. No significantly elevated RRs were reported for fish and meat intake. Relative risks were adjusted for sex, age, municipality, smoking, and energy intake.

No studies were found that analyzed dietary intake of NDEA and pharyngeal cancer.

Prostate cancer

Two studies examine dietary NDMA intake and prostate cancer risk (Loh et al. 2011; Jakszyn et al. 2012). No association was found by Loh and colleagues (2011) for dietary NDMA and prostate cancer (aHR=1.01; 95% CI 0.90-1.13). Jakszyn et al. (2012) utilized data from the previously described EPIC cohort. Dietary data was available for 139,005 men that were recruited from 8 European countries. The authors reported the following HRs for prostate cancer for quintiles of NDMA: Q2 (1.07; 95% CI 0.96-1.19); Q3 (1.05; 95% CI 0.94-1.17); Q4 (1.05; 95% CI 0.94-1.18); Q5 (1.04; 95% CI 0.92-1.18); the *p* for trend was non-significant at 0.95. All models were stratified by age, and center and adjusted for educational level, marital status, BMI, protein from dairy, smoking status, lifetime intensity of smoking, time since quitting smoking (for former smokers), and total energy intake. Some risk factors for prostate cancer, including race and family history of prostate cancer, were not adjusted for (ACS 2020a; Adami et al. 2018).

No studies were identified examining dietary NDEA intake and prostate cancer.

Summary of dietary NDMA studies and cancer

Several studies have been undertaken to examine dietary intake of NDMA and various cancers. The findings of most of these studies were null. Briefly, no studies showed an association of dietary NDMA exposure and breast cancer, prostate cancer, or head and neck (pharyngeal) cancer. The results of three studies on dietary NDMA and esophageal cancer were inconsistent. Two studies found no association with esophageal cancer. One study found an association of NDMA and squamous cell carcinoma of the esophagus but did not find an association for esophageal adenocarcinoma. The findings of the studies of lung cancer were inconsistent and the two studies that did report an association were case-control studies and suffered from various issues such as proxy response bias. All of the studies of lung cancer failed to adjust for potential important confounders such as secondhand smoke exposure and potential radon exposure. Only one study analyzed the association between dietary NDMA and pancreatic cancer; a significantly elevated risk was not found. The findings for colorectal and stomach/gastric cancers are inconsistent and are described in further detail later in this report.

Uncertainties and limitations of dietary studies

The studies examining dietary intake of NDMA and cancer suffer from serious limitations. The studies examining dietary intake from NDMA that are described above typically used FFQs. FFQs ask respondents how often and how much food they consumed over a specific period (Shim et al. 2014). Nasca and Pastides (2008) state regarding FFQs, “there is a growing concern that its weaknesses may outweigh its strengths.” Naska et al. (2017) indicate that FFQs are particularly prone to recall bias because “individuals are asked to report their intake retrospectively and usually refer to prolonged periods of time.” FFQs are also prone to recall bias from intentional misreporting of consumption of certain foods (Naska et al. 2017). Shim et al. (2014) states that measurement errors related to methodology are a limitation of FFQs.

Not only is exposure to certain foods estimated using FFQs, but the amount of NDMA in each food is also estimated. According to Naska et al. (2017), errors in exposure assessment can also be introduced when food composition databases are used to calculate intake. For example, in Loh et al. (2011), described below, NDMA and nitrite consumption was estimated by matching the food items in the FFQ to items in a food database developed by Jakszyn et al. (2004). Jakszyn et al. (2004) used studies published in various countries including the United Kingdom, the United States, Germany, France, India, and Hong Kong, to assign nitrates, nitrites, and

NDMA concentrations to various food items. Further, these studies could have been published as far back as 1980. Analytic methods, cooking methods, and types of foods consumed have changed considerably over the past 40 years, thus increasing the potential for exposure misclassification. As a result, the flaws inherent in the dietary studies prevents plaintiffs from establishing general causation.

Occupational Studies of Rubber Workers

It is improper to compare occupational studies of rubber workers and their potential NDMA exposure to the NDMA exposure experienced by individuals that consumed valsartan with NDMA impurity. Rubber workers are exposed to a variety of harmful substances, some of which are known to cause cancer. IARC (2012) concluded that there is *sufficient evidence* in humans for the carcinogenicity of occupational exposures in the rubber-manufacturing industry. IARC (2012) further states, however, "The rubber-manufacturing industry has used and still uses a wide variety of substances that belong to many different chemical categories, e.g. carbon black, aromatic amines, PAH, N-nitrosamines, mineral oils, other volatile organic compounds from curing fumes, trace amounts of monomers from synthetic rubber like 1,3-butadiene, acetonitrile, styrene, vinyl chloride, ethylene oxide, etc. For this reason, it has been difficult to relate the observed cancer hazards in the rubber-manufacturing industry *to exposure to specific chemical*" (Italics added for emphasis). Therefore, occupational studies of rubber workers were not considered in this report.

Analysis of Bradford Hill Criteria

The Bradford Hill criteria were first published in 1965 by Sir Austin Bradford Hill to assist in the determination of whether observed epidemiologic associations are causal (Fedak et al. 2015). The nine criteria are: strength, consistency, temporality, biological gradient, specificity, biological plausibility, coherence, experiment, and analogy (Hill 1965). The eighth criterion, experiment, is not applicable to the present analysis and was excluded from this analysis. The remaining criteria are described in further detail, below:

Strength: According to Hill (1965), the stronger an association is, the higher the likelihood of a causal relationship. Conversely, smaller associations are more likely to be caused by underlying contributors like bias and confounding and are therefore less suggestive of a causal relationship (Fedak et al. 2015).

Consistency: This criterion indicates that, to establish causality, an association should be consistently observed in studies conducted in different populations, places, circumstances, and time periods (Hill 1965).

Temporality: The criterion of temporality indicates that the exposure must precede the outcome (Hill 1965).

Biological gradient: A biological gradient, or a clear dose-response where disease linearly increases with increasing exposure, presents strong evidence of a causal relationship (Hill 1965).

Specificity: A strong argument of causation is provided when an association is limited to one exposure and outcome (Hill 1965).

Biological plausibility: It is helpful in determining causation if the association between the exposure and disease is biologically plausible (Hill 1965).

Coherence: The available data on the interpretation of cause-and-effect should not conflict with what is known about the natural history and the biology of the disease (Hill 1965).

Analogy: When there is strong evidence of a causal association between a specific exposure and a disease, then a similar exposure may cause a similar disease (Hill 1965).

For several of the cancers described above, there is no evidence of an observed association. In those instances, a Bradford Hill analysis was not carried out. However, for colorectal, liver, and stomach cancers, Bradford Hill analyses were undertaken and are described below.

Colorectal cancer

Strength: Regarding the studies of cancer and pharmaceuticals with NDMA impurity, the range of hazard ratios is 0.46 (95% CI 0.43-0.49) to 1.46 (95% CI 0.79-2.73). For the dietary studies, Loh et al. (2011) report adjusted hazard ratios of 0.99 (95% CI 0.83-1.18) and 1.46 (95% CI 1.16-1.84) for colon and rectal cancer, respectively; Zhu et al. (2014) report an OR of 1.42 (95% CI 1.03-1.96) for the highest quintile of NDMA intake; and Knekt et al. (1999) report an adjusted RR of 2.12 (95% CI 1.04-4.33) for the highest quartile of dietary NDMA. Many of the above risk estimates are non-significant and even selecting the highest risk estimates for the pharmaceutical and dietary studies, 1.46 and 2.12, do not provide evidence of a strong association between NDMA and colorectal cancer. More specifically, WHO (2000) indicates that relative risks that are greater than 1 and less than 1.5 show a "weak" strength of association and relative risks between 1.5 and 3.0 show evidence of a "moderate" strength of an association.

Consistency: As indicated in the assessment of the 'Strength' criterion above, there is a lack of consistent findings in the available studies.

Temporality: Zhu et al. (2014), a case-control study in Canada, used a food frequency questionnaire (FFQ) to assess dietary intakes one year prior to enrollment in the study (controls) or one year prior to colorectal cancer diagnosis (cases). A normal latency period for cancer is 15-20 years or longer (NIOSH 2012). A FFQ taken at the time when a person has cancer assessing dietary intake for the previous year does not satisfy the criteria of temporality.

Biological gradient: In their prospective cohort study, Knekt et al. (1999) did not find a significant trend when they examined colorectal cancer and NDMA intake by quartile (p for trend=0.47). In the analysis of quintiles of dietary NDMA intake and colorectal cancer, Zhu et al. (2014) did report a significant trend in their population-based case-control study (p=0.005). Therefore, the available studies are inconsistent regarding a dose-response between dietary NDMA intake and colorectal cancer.

Specificity: The plaintiffs are alleging that valsartan with NDMA impurity can cause a wide variety of cancers. In other words, they are refuting the argument of specificity which suggests that NDMA/NDEA has a signature effect. There is no clear evidence that NDMA exposure, whether through consumption of pharmaceuticals or typical dietary intake, is causally associated with colorectal cancer.

Biological plausibility: There is no evidence of an increased risk of colorectal cancer in humans to suggest that a mechanism exists by which this cancer occurs.

Coherence: The risk factors for colorectal cancer are well-defined and do not include NDMA exposure (ACS 2020b; Adami et al. 2018).

Analogy: The studies described above find no evidence of an increased risk of colorectal cancer and nitrite intake.

Liver cancer

Strength: Five studies examine liver cancer in association with pharmaceuticals and NDMA impurity. Kantor et al. (2021) report the highest hazard ratio for liver cancer, 1.91 (95% CI 1.09-3.36). However, this association was attenuated when regular ranitidine use was compared to regular omeprazole use (aHR=1.15; 95% CI 0.58-2.26). These hazard ratios do not provide strong evidence of an association. According to WHO (2000), a risk estimate of 1.15 would be considered "weak."

Consistency: In addition to Kantor et al. (2021), described above, Gomm and colleagues (2021) report an adjusted hazard ratio of 1.16 (95% CI 1.03-1.31) for "Exposure to NDMA-contaminated valsartan." However, Gomm et al. (2021) did not report a significantly elevated adjusted HR for long-term valsartan use (1.22; 95% CI 0.80-1.89). Yoon et al. (2021) did not report an elevated risk of liver cancer among ranitidine with NDMA impurity users compared to famotidine users (HR=0.85; 95% CI 0.69-1.05). Similarly, Kim et al. (2021) reported ORs less than 1 for their analyses of ranitidine vs. famotidine (OR=0.39; 95% CI 0.36-0.41) and of ranitidine vs. omeprazole (OR=0.81; 95% CI 0.76-0.86). Pottegård et al. (2018) could not obtain estimates for liver cancer because there were no liver cancer events among those exposed to NDMA impurity in valsartan. Therefore, the findings across studies are not consistent.

Temporality: The study populations described above did consume valsartan prior to the occurrence of the outcome. However, this criterion is moot since the other criteria do not support a cause-and-effect relationship between NDMA and liver cancer.

Biological gradient: Gomm et al. (2021) did not find a dose-response relationship when examining NDMA exposure by dose categories: 0 to ≤ 90 DDD (aHR=1.15; 95% CI 0.98-1.34); > 90 to ≤ 170 DDD (aHR=1.19; 95% CI 1.02-1.40); > 170 DDD (aHR=1.13; 95% CI 0.97-1.33).

Specificity: The plaintiffs are alleging that valsartan with NDMA impurity can cause a wide variety of cancers. In other words, they are refuting the argument of specificity which suggests that NDMA/NDEA has a signature effect. There is no clear evidence that NDMA exposure, whether through consumption of pharmaceuticals or typical dietary intake, is causally associated with liver cancer.

Biological plausibility: There is no evidence of an increased risk of liver cancer in humans to suggest that a mechanism exists by which this cancer occurs.

Coherence: The risk factors for liver cancer are well-defined and do not include NDMA exposure (ACS 2019c; Adami et al. 2018).

Analogy: There are no human studies of dietary or pharmaceutical intake that examine nitrosamine intake and liver cancer risk.

Stomach cancer

Strength: Regarding the pharmaceutical studies, Yoon et al. (2021) reported a hazard ratio for stomach or gastric cancer (HR=1.06; 95% CI 0.86-1.31) and Kim et al. (2021) reported ORs less than 1 for their analyses of ranitidine vs. famotidine (OR=0.43; 95% CI 0.36-0.51) and for ranitidine vs. omeprazole (OR=0.58; 95% CI 0.49-0.68). Song et al. (2015) report an overall meta-risk estimate of 1.34 (95% CI 1.02-1.76), although the heterogeneity (I^2=75.8%) was high.

These hazard ratios do not provide strong evidence of an association. These risk estimates indicate a "weak" strength of association (WHO 2000).

Consistency: Song et al. (2015) report separate meta-risk estimates for the cohort studies and case-control studies, separately. The HR for cohort studies, the superior study design, was non-significant (1.09; 95% CI 0.89-1.33) and the heterogeneity was low, indicating less variation and more consistency across study outcomes. On the other hand, the HR for the case-control studies was elevated (2.05; 95% CI 1.14-3.67) but the heterogeneity (I^2=88.6%) was very high, indicating uncertainty and inconsistency across study results. Therefore, overall the findings of these studies are inconsistent and more specifically, the studies that do report an association are also inconsistent.

Temporality: As indicated above, the studies that find an elevated risk of stomach cancer from dietary NDMA exposure tend to be case-control studies. According to Lewallen and Courtright (1998), "The temporal relationship between the supposed cause and effect cannot be determined by a case-control study." Therefore, the criterion of temporality is not met.

Biological gradient: Song et al. (2015) indicate that they conducted a dose-response analysis; the trend was nonlinear. Only four studies were included in the dose-response analysis by Song et al. (2015); Larsson et al. (2006); Keszei et al. (2013); LaVecchia et al. (1995); DeStefani et al. (1998). LaVecchia et al. (1995) and DeStefani et al. (1998) are older and are case-control studies. It is unclear why the 2006 study of Jakszyn and colleagues was not included in the dose-response analysis. Jakszyn et al. (2006) did not find a significant dose-response for dietary intake of NDMA and stomach cancer (*p* for trend=0.96).

Specificity: The plaintiffs are alleging that valsartan with NDMA impurity can cause a wide variety of cancers. In other words, they are refuting the argument of specificity which suggests that NDMA/NDEA has a signature effect. There is no clear evidence that NDMA exposure, whether through consumption of pharmaceuticals or typical dietary intake, is causally associated with stomach cancer.

Biological plausibility: There is no evidence of an increased risk of stomach cancer in humans to suggest that a mechanism exists by which this cancer occurs.

Coherence: The risk factors for stomach cancer, including *H. pylori* infection, are well-defined and do not include NDMA exposure (ACS 2021; Adami et al. 2018).

Analogy: Studies described herein found no evidence of an increased risk of stomach cancer and nitrite intake (e.g., Loh et al. 2011; Keszei et al. 2013; Pobel et al. 1995).

Discussion and Conclusions

The FDA estimated that if 8,000 people took the highest valsartan dose containing NDMA from the recalled batches daily for four years there *may* (italics added for emphasis) be one additional case of cancer over the lifetimes of the 8,000 people (FDA 2019a). The estimate for NDEA is 1 in 18,000 (FDA 2019a). Several published papers, as described above, describe allowable daily intake, permissible daily exposure, and tolerable daily intake values that are much higher than those of the FDA (Johnson et al. 2021; Snodin and Elder 2019; Fitzgerald and Robinson 2007). It is important to keep in mind that all these estimates are based on the results of animal studies, and the estimates of risk at low dose are *theoretical*.

According to 2016-2018 data from the National Cancer Institute, approximately 39.2% of men and women (i.e., 4 out of 10) will be diagnosed with some type of cancer during their lifetime (NCI Undated b). It would be impossible to detect a risk of 1 in 8,000 or 1 in 18,000 when the background risk is 4 in 10. That is also true for a rare cancer, such as pancreatic cancer, which has a lifetime risk of 1.7 in 100 (NCI Undated c).

Each cancer type has its own set of risk factors. Some factors increase the risk of many types of cancers. For example, smoking has been associated with 12 types of cancer including liver, lung, and bladder (CDC 2021a). Obesity, which is a major risk factor for hypertension, is associated with a higher risk of getting 13 types of cancer including liver and colorectal cancer; these 13 cancer types make up 40% of all cancers diagnosed in the United States annually (CDC 2021b).

Valsartan is taken for hypertension. A recent meta-analysis examined the association between blood pressure and various cancers and found significant associations between hypertension and several cancers including kidney, colorectal, endometrial, and esophageal cancer (Seretis et al. 2019). An association of valsartan and cancer could thus be confounded by the very reason for taking the drug in the first place.

The American Cancer Society (ACS) describes risk factors for cancer of different sites (e.g., lung, colorectum, pancreas). None of the studies described in this report have adjusted for all the potentially confounding factors described by ACS, and many did not adjust for some well-known risk factors (e.g., *H. pylori* and stomach cancer). Furthermore, none of the ACS descriptions of risk factors for various cancers mentions NDMA or NDEA. The results of the dietary studies were conflicting in many instances, and it cannot be concluded that there is a causal association between NDMA/NDEA intake and an increased risk of cancer in humans. The dietary results are consistent with the results of the pharmaceutical studies on valsartan and ranitidine. To summarize, there is no evidence that taking valsartan increases the risk of cancer.

Plaintiffs' Expert Reports

Expert Report of Mahyar Etminan

Dr. Etminan prepared a report for the plaintiffs in this case. In several places in his report Dr. Etminan displays a lack of knowledge of basic principles of epidemiology. He speculates on why studies failed to demonstrate an increased risk of cancer without any basis for his speculation. He criticizes studies that fail to demonstrate an increased risk of cancer for issues that are also true of the studies that he cites as evidence of an increased risk of cancer. He misunderstands some of the Bradford Hill criteria. Furthermore, he misunderstands what odds ratios (OR) are. The OR represents the odds that an outcome will occur given a particular exposure compared to the odds of the outcome occurring in the absence of exposure. It should not be used to indicate a % increase in risk. That is taught in the beginning course in epidemiology. Yet Dr. Etminan repeatedly makes this mistake throughout his report. For example, with respect to his description of the study by Rogers et al. (1995) he states that an OR of 1.82 signifies an 82% increase in risk. Throughout his report, he indicates that the amount of NDMA in one 320 mg tablet could be 52,500 ng. The highest NDMA in any Valsartan tablet was reported to be 20,190 ng (FDA 2019a).

Occupational Studies

Dr. Etminan focuses considerable attention in his report on a mortality study of rubber workers in the United Kingdom (Hidajat et al. 2019). As described earlier in this report, rubber workers are not a comparable population to individuals consuming valsartan with NDMA impurity.

A mortality study of the same cohort of rubber workers in Hidajat et al. (2019) was conducted by McElvenny et al. (2018). The length of follow-up in both studies was the same (49 years). McElvenny et al. (2018) reported significantly increased standardized mortality ratios (SMRs) for all cancer, stomach cancer, lung cancer, and bladder cancer. Dr. Etminan claims that Hidajat et al. (2019) found significantly increased mortality for "stomach, esophageal, pancreatic, bladder, liver, lung, prostate, and blood cancers (lymphoma, leukemia, myeloma)." He then criticizes McElvenny et al. (2018): "Due to the sample size of the study, other cancers did not demonstrate a statistically significant increase in risk mainly due to small sample sizes." McElvenny et al. (2018) and Hidajat et al. (2019), however, were studies *of the same cohort with the same length of follow-up*. Dr. Etminan further opines that the study cohort of McElvenny et al. (2018) might have been exposed to carcinogens other than NDMA/NDEA and thus the cancer risk that could be allocated to NDMA/NDEA is low. The same exposure to carcinogens other than NDMA/NDEA could also be said for Hidajat et al. (2019). As Hidajat et al. (2019) themselves stated, "cross-contamination between departments could not rule out the need for multipollutant models but given the high correlation between exposures this requires different and complex statistical modeling, with currently unknown validity in this context." Again, as IARC (2012) stated, rubber workers are exposed to a variety of substances, and it is difficult to relate cancer hazards to any specific chemical.

Dr. Etminan acknowledged the lack of smoking data in the Hidajat et al. (2019) study but accepted Hidajat et al.'s "additional simulations" using data from a different cohort of rubber workers to determine that smoking was "likely not a significant confounding factor." The cohort that Hidajat and colleagues utilized smoking data from included information on smoking prevalence, ex-smokers, and never smokers from a cohort of rubber industry workers after 1982 and cite DeVocht et al. (2005) as the source. There are no data on smoking in DeVocht et al. (2005), however. DeVocht et al. (2005) collected exposure data in the rubber manufacturing industry from Germany, UK, the Netherlands, Sweden, and Poland into a single occupational hygiene database. The date of first employment in the cohort studied by Hidajat et al. (2019) and McElvenny et al. (2018) ranged from prior to 1930 through 1966. McElvenny et al. (2018) stated, "In the present study, there was a highly statistically significant trend for increasing lung cancer SMRs from those first employed in the industry before 1930 through to those first employed in the 1960s, which mirrors the general rise of per capita tobacco product use in the UK." It is obvious from the statement by McElvenny et al. (2018) that smoking could have had a considerable effect on cancer mortality for the cohort. Even if the source of the data on smoking prevalence cited by Hidajat can be identified, data collected after 1982 should not be used to estimate prevalence of smokers, ex-smokers, and nonsmokers for a cohort that was first employed well before 1982.

An occupational study of rubber workers by Straif et al. (2000) found that all cancer mortality (RR=1.4; 95% CI 1.0-1.8) and cancer mortality of the lip, oral cavity, and pharynx (RR=5.1; 95% CI 1.2-20.6) were significantly elevated in the high nitrosamines exposure category. Cancer mortality for other sites was not significantly elevated. Included in Dr.

Etminan's comment on Straif et al. (2000): "However, this study did not control for all potential confounding variables (such as death due to competing cancers)..." A competing cancer is not a confounding factor.

In Table 1 of Dr. Etminan's report, he presents the magnitude of hazard ratios needed to "eliminate the increased risk of cancer" in Hidajat et al. (2019). He estimated the hazard ratios using E-value methodology, which he describes as a "published validated method that can show the hazard ratio needed to reverse the positive findings for a study due to the effect of the unmeasured confounder." The E-value methodology is not without controversy; see comments by Ioannidis et al. (2019). Even if the methodology were appropriate, the study by Hidajat et al. was a mortality study with virtually no information on risk factors such as smoking, alcohol consumption, *H. pylori* infection, obesity, and family history. The risk of lung cancer in smokers is over 10-fold greater than in nonsmokers (CDC 2014). Vohlonen et al. (2016) found the risk ratio of stomach cancer to be 5.8 in men with *H. pylori* infection compared to men with healthy stomachs. A family history of pancreatic cancer in a first-degree relative is associated with an increased risk of pancreatic cancer of between 2.5 to 5.3 times Hart et al. (2006). These risks would have easily eclipsed the risks derived by Dr. Etminan's E-value methodology approach.

Discussion by Cancer Type

Stomach cancer

In his discussion of stomach cancer and dietary NDMA, Dr. Etminan reports that the hospital-based case-control study of LaVecchia et al. (1995) found that those who "took" ≥ 190 ng NDMA/day had an odds ratio (OR) for stomach cancer of 1.37 (95% CI 1.1-1.70) compared to those "taking" ≤130 ng NDMA/day after controlling for some potential confounding variables including family history of stomach cancer. Important confounding variables not controlled for include *H. pylori*, smoking, obesity, heavy consumption of alcohol, and previous stomach surgery. Dr. Etminan also describes the Larsson et al. (2006) cohort study of women and reports that the relative risk of stomach cancer in the highest NDMA exposure category was 1.96 (95% CI 1.08, 3.58) compared to the lowest exposure category. While this may be true, Larsson et al. (2006) were not convinced that the association was real. They concluded, "Our findings suggest that high consumption of processed meat may increase the risk of stomach cancer. Dietary nitrosamines might be responsible for the positive association."

Another study on stomach cancer described by Dr. Etminan is the hospital-based case-control study of stomach cancer by DeStefani et al. (1996). He reports that those "taking NDMA at doses greater than or equal to 270 ng/day had a 3.62 (OR=3.62, 95% CI:2.38-5.51) times or 262% increase in the risk of gastric cancer compared to those taking 140 ng or less per day." He states that a possible limitation of the study is that it did not control for prior history of stomach cancer. He neglects to mention that the study did not control for a variety of other risk factors as well including *H. pylori*, obesity, previous stomach surgery, and family history of stomach cancer.

The cohort study by Loh et al. (2011) failed to find a significant increase in the risk of gastric cancer. Dr. Etminan explained this by stating, "However, given the imprecise estimates of the risk provided by these studies, one cannot exclude the possibility that a risk might exist, and that the statistically insignificant results might have been due to a small sample size resulting in an inadequate number of stomach cancer cases in this study compared to the disproportionally larger number of variables adjusted in the model, which possibly led to imprecise estimates." This is total speculation. The sample size was not small; there were 23,363 men and women in

the cohort. He also claims that there may have been too many variables in the model. The number of variables speaks to the quality of the analysis. In many of the studies claimed by Dr. Etminan as demonstrating evidence of a cancer risk, risk factors known to be associated with the specific cancer are not even addressed.

Dr. Etminan describes the Jakszyn et al. (2006) cohort study of 521,457 individuals in Europe. The average follow-up was 6.64 years. The study found "no association between NDMA intake and gastric cancer risk." Dr. Etminan states that "a material limitation of this study is that it included mostly older adults but a description of other comorbid conditions (conditions such as heart disease or diabetes) which are extremely common and complex in older study populations, were not provided." The subjects in the study were age 35-70 years old. The American Cancer Society (2021) states that most people who get stomach cancer are in their 60s, 70s, and 80s. Follow-up was done with cancer registries, which do not provide information on heart disease or diabetes. It is unclear, however, why Dr. Etminan believes heart disease or diabetes are critical to the evaluation of the results. He certainly did not make that criticism of studies that he claims found an association of NDMA and stomach cancer. His apparent explanation is that "it is possible that subjects with a higher prevalence of comorbid conditions died as a result of these conditions and did not have the opportunity to develop stomach cancer." That is sheer speculation. Furthermore, people do die of causes other than cancer. Had they lived longer, would they have developed cancer, or more specifically, died of stomach cancer? Again, that is sheer speculation. Dr. Etminan claims that the study did not control for important confounders such as "history of stomach cancer." The study controlled for sex, height, weight, education level, tobacco smoking, cigarette smoking intensity, work and leisure physical activity, citrus and non-citrus fruits intake, vegetables intake, energy intake and nitrites. That is considerably more variables than what were controlled for in the studies cited by Dr. Etminan as demonstrating evidence of stomach cancer risk.

Keszei et al. (2013) conducted a cohort study in the Netherlands to examine the risk of nitrosamines on gastric and esophageal cancer subtypes. The follow-up was 16.3 years. The authors found that the hazard ratio (HR) for a 0.1 µg/d increase in intake of NDMA in males was 1.06 (95% CI 1.01-1.10) for gastric non-cardia adenocarcinoma (GNCA). The trend across tertiles of intake of NDMA was not significant ($p = 0.09$) for GNCA in males. There was no association of gastric cancer adenocarcinoma (GCA) with NDMA intake. There was no association of NDMA intake and either GCA or GNCA in women. Dr. Etminan attempts to explain away the results of Keszei et al. (2013) by stating, "The lack of an effect in this study might be explained by potential for misclassification (inaccurate reporting of different food intake by the subjects) of the diet questionnaire used in the study as stated by the authors." Studies that Dr. Etminan claims show evidence of an association of NDMA intake and increased risk of gastric and other cancers also relied on food frequency questionnaires. Dr. Etminan claims that Keszei et al. (2013) "did not report the number of subjects lost to follow up which would no longer put them at risk of developing gastric cancer and potentially underestimate the true risk of gastric cancer in this study." In the "Subjects and Methods" section, Keszei et al. (2013) state that only one subcohort member was lost to follow-up. Keszei et al. (2013) was a study of a subcohort, not the full cohort.

Knekt et al. (1999) conducted a cohort study to examine the relationship between intake of nitrates, nitrites, and NDMA cancer of the gastrointestinal tract. The authors found no evidence of an increased risk of stomach cancer with NDMA intake (RR = 0.75, (5% CI 0.37,

1.51). Dr. Etminan states, "However, the study's wide confidence intervals did not exclude a harmful effect of up to 51% as it only had 68 total stomach cancer cases and it is likely that when these numbers were broken down to categorize NDMA to high vs low categories of exposure, the study potentially lost statistical power to adequately assess this risk. Later in his report, he hails Knekt et al. (1999) for finding an increased risk of colorectal cancer in the high exposure category. The number of colorectal cancer cases in Knekt et al. (1999) was 73 (vs. 68 stomach cancer cases).

A hospital case-control study by Pobel (1995) reported an OR of 7.0 for the third tertile of NDMA intake (OR = 7.00, 95% CI 1.85-26.46). The OR was adjusted for age, sex, occupation, and total calorie intake. The American Cancer Society (ACS) recognizes many risk factors for stomach cancer including gender, age, ethnicity, *H. pylori* infection, being overweight or obese, alcohol use, tobacco use, previous stomach surgery, some types of stomach polyps, and pernicious anemia, family history of stomach cancer, Type A blood to name a few (ACS 2021). The ACS indicates diet is a risk factor but does not mention NDMA. Dr. Etminan states, that "Although this study did not control for history of stomach cancer, the large magnitude of this association makes it unlikely that unmeasured confounders would have changed the results of this study to a null association." Dr. Etminan should be aware that ORs exaggerate the size of an effect compared with relative risks (Davies et al. 1998). Furthermore, it is interesting that Dr. Etminan is willing to waive "unmeasured confounders" in this small (92 cases, 128 controls) but criticizes Jakszyn et al. (2006) for not controlling for "important confounders such as history of stomach cancer." Is it because Jakszyn et al. (2006) found no association between NDMA intake and stomach cancer?

Finally, with respect to stomach cancer, Dr. Etminan describes a meta-analysis of 11 epidemiologic studies by Song et al. (2015). Dr. Etminan reports that the stomach cancer meta-RR for NDMA intake was 1.34 (95% CI 1.02-1.76). He neglects to state, however, that the RR for the cohort studies was not significantly elevated (RR=1.09, 95% CI 0.89-1.33) and the RR for the population-based case control studies was not elevated (RR=1.10, 95% CI 0.8-1.5). Only the RR for hospital-based case-control studies was elevated (RR=2.81, 95% CI 1.16, 6.80). Dr. Etminan should be aware of Berkson's bias, a well-known issue of hospital-based case-control studies (Sutton-Tyrell 1991). Dr. Etminan also neglects to mention that the RR for NDMA intake was not significantly elevated (RR=1.30, 95% CI 0.97-1.75) for the highest quality studies.

Dr. Etminan concludes that the evidence from dietary epidemiologic studies demonstrate that there is a "probable" increase in the risk of stomach cancer with high NDMA intake. However, it is important to keep in mind that the evidence primarily comes from hospital-based case-control studies. One cohort study (Larsson et al. 2006) found an association of NDMA intake and stomach cancer, but the authors don't go so far as to conclude the association is real. Jakszyn (2006), a cohort study of over a half million people, which is the largest study ever conducted on dietary intake of NDMA, found no evidence of an increased risk of stomach cancer. Two other cohort studies of dietary intake of NDMA also found no evidence of an increased risk of stomach cancer; a third found some evidence in males but not in females. The Song et al. (2015) meta-analysis does not report a significantly increased RR for stomach cancer for either cohort studies or population-based case-control studies, and it reports a high degree of heterogeneity for the hospital-based case-control studies. Dr. Etminan's belief that there is a "probable" increased risk of stomach cancer from dietary intake of NDMA is unfounded.

Colorectal cancer

Dr. Etminan states that the occupational study by Straif et al. (2000) found an increased risk of colon cancer mortality with nitrosamine exposure but due to the limited number of subjects there were not enough events to produce a statistically significant risk (RR=1.5, 95% CI 0.5-4.7). He also states that no risk for rectal cancer mortality (RR=0.8, 95% CI 0.2, 3.9) was observed but the "wide confidence intervals (due to only 19 deaths due to rectal cancers) including an upper bound of 3.9 does not exclude an increase in risk." Such statements are fanciful speculation. Dr. Etminan has no idea, had there been more colon or rectal cancer deaths, what the results would have been.

Dr. Etminan describes the population-based case-control study by Zhu et al. (2014) as demonstrating evidence of an increased risk of colorectal cancer associated with NDMA (OR=1.42, 95% CI 1.03, 1.96). A food frequency questionnaire was used to assess dietary intake 1 year before enrollment in the study (controls) or 1 year before colorectal cancer diagnosis (cases). If colorectal cancer takes years from exposure until development of the disease, the relevance of a questionnaire asking about dietary habits one year prior to diagnosis is questionable.

The cohort study by Knekt et al. (1999) found an increased risk of risk of colorectal cancer in the highest NDMA exposure group compared to the lowest exposure group (RR=2.12, 95% CI 1.04-4.33). It is curious that Dr. Etminan questions the reliability of the NDMA intake data for the stomach cancer results in Knekt et al. (1999) but fails to question the reliability of the NDMA intake data with respect to colorectal cancer. Dr. Etminan reports that the colorectal cancer results were adjusted for sex, age, municipality, smoking, and energy intake. Other risk factors for colorectal cancer per ACS (2020a), which the study did not adjust for, are obesity or overweight, physical activity, alcohol use, history of polyps or colorectal cancer, family history of colorectal cancer or polyps, and personal history of inflammatory disease.

Loh et al. (2011) was a cohort study of 23,363 men and women in the United Kingdom that examined the relationship between dietary intake of preformed N-nitroso compounds (NOCs), endogenous NOC, and nitrite and cancer incidence. The study did not report a significantly increased hazard ratio for colon cancer per NDMA S.D. (HR=0.99, 95% CI (0.83-1.18) but did report an increased risk of rectal cancer per NDMA S.D (HR=1.46, 95% CI 1.16-1.84). Dr. Etminan claimed that a limitation of the Loh et al (2011) study is "that it did not control for competing events such as a heart attack or stroke which would prevent a subject from being diagnosed with cancer and potentially leading to a smaller number of events." Cancer cases were ascertained by the East Anglican Cancer Registry and were flagged by the National Health Service Central Register for death and cancer incidence. Even if a study participant experienced a heart attack or stroke, that would not preclude the cancer case from being recorded in the Registry or the National Health Service Central Register.

Dr. Etminan concludes that the evidence from dietary epidemiologic studies demonstrate that there is a "probable" increase in the risk of colorectal cancer with NDMA intake. There is a lack of consistency among the results of the studies and the strength of the associations are either moderate or weak. The criterion of temporality has not been met in Zhu et al. (2014). As indicated above, Knekt et al. (1999) state "Although the association between nitrosamine intake and colorectal cancer observed here is plausible, it cannot be excluded that it may be due to confounding." Dr. Etminan's conclusion that there is a probable increase in risk in colorectal cancer with NDMA intake is unsubstantiated.

Pancreatic Cancer

Dr. Etminan describes two studies that evaluated the risk of pancreatic cancer and exposure to nitrosamines, NDMA, or NDEA (Fritschi et al. 2015; Zheng et al. 2019). Fritschi et al. (2015), a population-based control study that examined whether occupational exposure to N-nitrosamines and pesticides increased the risk of pancreatic cancer, did not find an association for N-nitrosamines. Dr. Etminan explains this finding by stating that "nitrosamines are comprised of compounds other than NDMA and NDEA, many of which might be less potent carcinogens than NDMA and NDEA, and some of which are considered to be potentially non-carcinogenic, the grouping of nitrosamines as a class would have likely diluted the carcinogenic effect incurred as a result of NDMA or NDEA exposure."

A case-control study of pancreatic cancer cases by Zheng et al. (2019) examined the association with dietary N-nitroso compounds including NDMA and NDEA. Dr. Etminan reports that the authors found an OR = 2.28 (95% CI 1.71-3.04) in the highest exposure category for NDEA. The OR for NDMA in the highest exposure category was not significant. Dr. Etminan does not attempt to explain why NDMA failed to show an association with an increased risk of pancreatic cancer.

Dr. Etminan concludes that the preponderance of dietary and occupational epidemiologic evidence demonstrates a probable increase in the risk of NDMA and NDEA with pancreatic cancer. As described above, the occupational studies of rubber workers that Dr. Etminan cites in his conclusion cannot be included in an assessment of the carcinogenicity of NDMA because of the multiple substances including known carcinogens to which rubber workers are exposed. He discounts the population-based study by Fritschi et al. (2015), a large population-based case-control study of pancreatic cancer, which found no evidence of occupational exposure to N-nitrosamines and pancreatic cancer. He claims that N-nitrosamines include compounds besides NDMA and NDEA, and these compounds may be less carcinogenic than NDMA/NDEA or even noncarcinogenic. A hospital-based case control-study of pancreatic cancer by Zheng et al. (2019) reported a significantly elevated OR for NDEA intake (2.28, 95% CI 1.71-3.04), but the OR for NDMA was not significantly elevated. Dr. Etminan presented one study that found an association of NDEA and pancreatic cancer, and on that one study he concludes that NDEA increases the risk of pancreatic cancer. His conclusion that the epidemiologic evidence demonstrates an increased risk of NDMA and NDEA with pancreatic cancer is unsupported.

Head and Neck Cancers – Pharynx, Larynx, and Esophageal

Dr. Etminan mistakenly includes esophageal cancer with head and neck cancers. Head and neck cancer includes cancer of the oral cavity, the throat (pharynx), the voice box (larynx), the paranasal sinuses and nasal cavity, and salivary glands (NCI 2021). Because Dr. Etminan has included esophageal cancer in this group, his comments on the studies on esophageal cancer will be addressed here.

The study by Loh et al. (2011), described previously, did not find a significantly increased risk of esophageal cancer (HR=1.13, 95% CI 0.77-1.68). Dr. Etminan's explanation for the non-statistically significant finding is "probably due to the small number of cases (55) compared to the large number of covariates (9 variables) used to adjust for potential confounding in this study." Loh et al. (2011) was a study of 23,363 men and women. He then claims that because the upper confidence limit was 1.68, it meant that "a 68% increased risk of esophageal cancer could not be ruled out." Using that argument, one could state that based on the lower limit of 0.77, a 23% decrease in risk could not be ruled out. The correct interpretation is that the

confidence limits around the HR include 1.0; therefore, the HR is statistically no different from the null.

Dr. Etminan claims that the population-based case-control study by Rogers et al. (1995) found an OR for oral cancer of 1.82 (95% CI 1.10-3.00) or an "82% increase in risk" for the highest NDMA exposure category. Dr. Etminan then claims that oral cancers are a "combination of esophageal, laryngeal, and possibly other oral cancer types." That is false. Oral cancers include the lips, the front two-thirds of the tongue, the gums, the lining inside the cheeks and lips, the floor of the mouth under the tongue, the hard palate, and the small area of the gum behind the wisdom teeth. Rogers et al. (1995) found that neither the OR for cancer of the larynx or cancer of the esophagus were significantly elevated.

Dr. Etminan reports that the cohort study by Keszei et al. (2013) found significantly increased HRs for esophageal carcinoma in both men and women. Keszei et al. (2013) reported significantly elevated HRs for esophageal squamous cell carcinoma in men and women but did not report significantly elevated esophageal adenocarcinoma in men and women.

Dr. Etminan concludes that "Based on the totality of the evidence in occupational and dietary studies it is probable that high exposure to NDMA increases the risk of head and neck cancers." The concerns of including occupational studies of rubber workers in the evaluation of NDMA and risk of cancer have previously been raised. Loh et al. (2011) and Rogers et al. (1995) did not find associations of NDMA intake and esophageal cancer. Keszei et al. (2013) found a significant relationship between NDMA intake and esophageal squamous cell carcinoma but not esophageal adenocarcinoma. A claim that NDMA intake is associated with esophageal cancer is groundless. Only one study reported an association between NDMA intake and oral cancer, the population-based case control study by Rogers et al. (1995). This single finding is not sufficient to conclude that NDMA intake is associated with an increased risk of head and neck cancer.

Liver cancer

Regarding liver cancer, Dr. Etminan cites the occupational study of Hidajat et al. (2019) as providing "the strongest evidence on the risk of liver cancer as it followed subjects for 49 years and was able to show a dose-response relationship (high vs. low). Again, Hidajat et al. (2019) is an occupational mortality study of rubber workers who are exposed to a variety of substances, some of which are known to cause liver cancer, specifically (e.g., vinyl chloride). Furthermore, McElvenny et al. (2018) reported no evidence of an increased SMR for either liver cancer or disease of the liver in the same cohort followed for the same number of years studied by Hidajat et al. (2019). Accordingly, Dr. Etminan's conclusion on this point is equally unsubstantiated.

Bladder Cancer

Dr. Etminan reports that Jakszyn et al. (2011), a large (481,419 participants) cohort study of diet and bladder cancer, found a statistically nonsignificant increased risk of bladder cancer in the highest NDMA exposure group (RR= 1.12, 95% CI: 0.88-1.44)[8]. There was no evidence of trend across exposure groups (p=0.49). Despite the nonsignificant increased HR in the high exposure group and the lack of dose response, Dr. Etminan reported that an increased risk "of up to 44% could not be ruled out." By the same logic, based on the lower limit of 0.88, a decreased risk of 12% could not be ruled out. The conclusion of Jakszyn et al. (2011) is "Our findings do

[8] Jakszyn et al. (2011) reported hazard ratios (HRs) not relative risks (RR).

not support an effect of red meat intake, nitrosamines (endogenous or exogenous), or heme iron intake on bladder cancer risk."

Dr. Etminan reports that Hidajat et al. (2019) found a statistically significant increased risk of bladder cancer in the highest NDMA exposure group in the cohort of rubber workers studied by Hidajat et al. (2019). Again, rubber workers are exposed to a variety of substances including aromatic amines, which are known to be associated with an increased risk of bladder cancer (Pira et al. 2010). Hidajat et al. (2019) had no smoking data for the cohort. Smoking is also a known risk factor for bladder cancer (ACS 2019a). McElvenny et al. (2018), a study of the same cohort studied by Hidajat et al. (2017) did not find a significantly elevated SMR for bladder cancer.

Despite the lack of an association of NDMA exposure and bladder cancer risk in Jakszyn et al. (2011) and the multiple exposures including known carcinogens (e.g., aromatic amines) experienced by rubber workers and the lack of smoking data in Hidajat et al. (2019), Dr. Etminan concludes that "high exposure to NDMA increases the risk of bladder cancer." Again, this conclusion is baseless.

Prostate Cancer

Dr. Etminan reports that Loh et al. (2011) did not find a significantly elevated risk of prostate cancer and NDMA exposure in a cohort study that included 10,783 men. Dr. Etminan explains this away by stating, "However, Loh was not designed to study only prostate cancer (looked at 9 cancers in total)." Loh et al. (2011) is a cohort study. One of the advantages of a cohort study is that multiple outcomes can be evaluated. Dr. Etminan also states that the study did not adjust "for previous history of prostate cancer, which is significant as prostate cancer is a recurring disease and men who experience a recurrence might die due to prostate cancer and not develop bladder cancer (sic)." Case ascertainment was done through the East Anglican Cancer Registry and the National Health Service Central Register. Thus, initial cases of prostate cancer would be reported to the Cancer Registry and the National Health Service. It is unclear why he is concerned in his discussion of prostate cancer about bladder cancer.

Jakszyn et al. (2012), a cohort study of dietary intake of nitrosamines and heme iron intake and prostate cancer in 139,005 males in 8 European countries did not find a significantly increased risk of prostate cancer for any quintile, including the highest NDMA exposure group; the *p* for trend (0.95) was also non-significant. Dr. Etminan explains the lack of statistical significance by stating, "However, the study by Jakszyn, like the study on bladder cancer by the same authors, provided no information on the comorbidity profile of the subjects as subjects with more comorbid conditions (heart disease) could have died prior to developing or being diagnosed with prostate cancer. This potential limitation is accentuated by the long 10-year follow up of the study which does increase the possibility of death due causes other than prostate cancer." It is total speculation by Dr. Etminan to assume that persons who died would have developed prostate cancer had they lived long enough.

Dr. Etminan cites Hidajat et al. (2019), a cohort mortality study of rubber workers, as demonstrating an increased risk of prostate cancer. A study of the same cohort by McElvenny et al. (2018) did not report an increased SMR for prostate cancer. As described above, rubber workers are exposed to a variety of compounds, some of which are known human carcinogens. Dr. Etminan's conclusion that an increased risk of prostate cancer is associated with exposure to

NDMA based solely on the occupational study of rubber workers by Hidajat et al. (2019) is baseless.

Blood Cancers – Lymphoma, Leukemia, and Multiple Myeloma

Dr. Etminan based his conclusions on blood cancers on two studies, both of which focused on occupational exposure. He considered a third study, Straif et al. (2000) to be too "underpowered" to be able to detect a risk of blood cancer. According to Dr. Etminan, a case-control study by Richardson et al. (2008) found "'a doubling of risk' of lymphoma (OR=2.22, 95% CI 1.48, 3.35) with exposure to nitrites, nitrates, or nitrosamines (all three combined)." Exposure to NDMA was not recorded in the study. Richardson et al. (2008) stated that "Analyses of the association between potential exposure to each of the 50 occupational agents and disease risk were conducted one occupational agent at a time, as opposed to deriving effect estimates that simultaneously adjusted for potential exposures to all other assessed agents." Agents were described as chemical, physical, and biological agents. There were 23 occupational categories considered; analyses were only adjusted for smoking. Thus, any conclusion with respect to nitrites, nitrates, or nitrosamines combined, let alone NDMA, could be confounded by a host of other "occupational agents" or risk factors for NHL that were not adjusted for. Hidajat et al. (2019) reported an increased risk of death due to leukemia and multiple myeloma (HR=3.47, 95% CI: 2.35-5.13; HR=2.81, 95% CI: 2.17-3.64, respectively) in the highest NDMA exposure category. The problems of using Hidajat et al. (2019) on which to base conclusions on NDMA exposure and cancer risk are described above. A conclusion that NDMA is associated with an increased risk of blood cancer based on the studies described above is totally without merit.

Lung Cancer

Dr. Etminan reports that DeStefani et al. (1996) conducted a lung cancer case-control study evaluating dietary intake of NDMA and found an "increased risk" of lung cancer (OR=3.14; 95% CI 1.86-5.29) in the highest NDMA exposure group compared to the lowest exposure group. DeStefani et al. (1996) is a hospital-based case control study in Montevideo, Uruguay. Patients were identified between May 1994 and December 1995. Dietary data were collected by a food-frequency questionnaire, which estimated the usual diet during the preceding five years. NDMA content of the food was estimated based on analyses of food in the United Kingdom, France, Canada, and the United States. Determination of NDMA in the foods based on values reported for countries not even on the same continent and for the most part, collected almost 20 years previously makes the estimates of NDMA in DeStefani et al. (1996) questionable at best. Furthermore, if the development of lung cancer takes years from exposure until development of the disease as it does for smoking and lung cancer, how relevant is a questionnaire asking about dietary habits five years prior to disease diagnosis? Again, Dr. Etminan should also be aware of the concerns of hospital-based case-control studies (described previously).

Dr. Etminan also reports that the Goodman et al. (1992) population-based case-control study of lung cancer and diet found an OR=3.3 (95% CI 1.7-6.2), described by Dr. Etminan as a 230% increase, and an OR=2.7 (95% CI 1.0-6.9, described by Dr. Etminan as "a 170% increase" in males and females, respectively. Dr. Etminan states that a limitation of Goodman et al. is that it is unclear how duration of exposure to nitrosamines was assessed. The diet questionnaire elicited information on over 130 food items along with three serving sizes. The reference period was one year before diagnosis or onset of symptoms and during the corresponding period for the matched controls. Additionally, this study is subject to proxy response bias described earlier in

this report. No information was provided by Goodman et al. (1992) on how NDMA intake was determined. If the development of lung cancer takes years from exposure until development of the disease as it does for smoking and lung cancer, how relevant is a questionnaire asking about dietary habits one year prior to disease diagnosis?

Finally, Dr. Etminan indicates that Hidajat et al. (2019), an occupational study of rubber workers, found an association of NDMA exposure and lung cancer risk. As indicated above, rubber workers have exposure to multiple substances including known human carcinogens, and Hidajat et al. (2019) did not have smoking data. Dr. Etminan's claim that it is "probable" that high exposure to NDMA based on the two dietary studies and the occupational study by Hidajat et al. (2019) is unfounded.

Pharmaceutical Studies by Pottegård et al. (2018) and Gomm et al. (2021)

Dr. Etminan acknowledges that Pottegård et al. (2018) did not find an increased risk of cancer among 5150 subjects taking valsartan and proceeds to enumerate a variety of reasons why this is so. He also argues that the risk could be as high as the upper bound of the confidence interval. By the same argument, it could be debated that valsartan is protective of cancer if we use the lower bound. He also argues that subjects in the study could have died due to cardiovascular disease and were no longer at risk of developing cancer; this is pure speculation.

Dr. Etminan reports that Gomm et al. (2021) found no evidence of an overall risk of cancer with NDMA use but did find a significant increase in risk of liver cancer (HR=1.16; 95% CI 1.03-1.31). Nevertheless, he criticizes the study for the short follow-up, "which is woefully inadequate to detect all cancer formations that would result from NDMA exposure." The follow-up was as long as possible given when exposure to valsartan with NDMA impurity occurred. He provides similar explanations for why Gomm et al. (2021) failed to show an increased risk of cancer as he did for Pottegård et al. (2018).

Bradford-Hill Criteria

Temporal Relationship

Dr. Etminan claims that in "all the studies that assessed the effect of NDMA (dietary or occupational) the effect of NDMA on the 9 different types of aforementioned cancers, NDMA exposure was measured prior to the diagnosis or death due these different cancers." That is simply not true. Many of the studies that Dr. Etminan cites are case-control studies, where patients with cancer were asked to complete a food frequency questionnaire. The amounts of NDMA in the food was then estimated from other sources. NDMA was not measured in the food as Dr. Etminan suggests. Furthermore, whether a food frequency questionnaire, taken at the time when a person has cancer, applies to 15-20 years prior (a normal latency period for cancer following exposure to a carcinogen) is highly questionable (NIOSH 2012).

Biological Plausibility

Dr. Etminan claims that "multiple regulatory agencies including IARC[9] have classified NDMA as carcinogenic" and that this classification has been "granted" in part due to an abundance of published animal studies that have been shown "through a mechanism of genotoxicity" to cause different cancers in animals. Biological mechanism is intended to assist in the determination of whether the epidemiologic data demonstrate a causal association. The

[9] IARC is not a regulatory agency. It does not issue regulations.

epidemiologic data don't demonstrate that NDMA is associated with an increased risk of cancer; thus mechanistic theories are interesting but no substitute for epidemiologic evidence.

Analogy

Dr. Etminan argues that nitrites are chemically like N-Nitrosodimethylamine and that nitrites "have been shown to increase the risk of cancer." He cites Coss et al. (2004) as evidence that nitrites cause cancer in humans. Coss et al. (2004) is a population-based case-control study of pancreatic cancer. None of the odds ratios were significantly elevated for the categories of dietary nitrite exposures in both men and women. The odds ratios were significantly elevated for some exposure categories of "dietary NDMA from animal sources," but there was no evidence of a dose response. The authors concluded that "the consumption of dietary nitrite from animal products may increase [pancreatic cancer] risk." The evidence described above by Dr. Etminan does not indicate that NDMA is associated, much less causally associated, with an increased risk of pancreatic cancer. The study by Coss et al. (2004) also cannot be said to demonstrate that nitrites are associated with an increased risk of pancreatic cancer. Like the criterion of biologic mechanism, analogy is intended to assist in the determination of whether the epidemiologic data demonstrate a causal association, not the other way around.

Dose Response Analysis

Dr. Etminan cites Hidajat et al. (2019) as providing evidence of a dose-response relationship between NDMA and 9 types of cancer. Again, Hidajat et al. (2019) is a study of rubber workers exposed to numerous substances including known carcinogens. It cannot be used to evaluate whether a causal association exists between NDMA and any type of cancer.

Specificity

Dr. Etminan correctly believes that the criterion of specificity does not play a role in evaluating whether NDMA/NDEA are causally associated with an increased risk of cancer.

Consistency

Consistency is the second of Bradford Hill's (1965) criteria. Dr. Etminan states that there is "scientific evidence suggesting that NDMA can cause cancer in animals for all 9 types of cancer." It is clear from Hill (1965) that consistency is meant to apply to epidemiologic data, not animal data. Dr. Etminan further claims that the epidemiologic evidence provide evidence that there is an increased risk of nine different types of cancer yet his Figure 1 ("Forest plot of dietary studies of NDMA/NDEA with different type of cancers") shows mixed evidence for different types of cancer and for some cancer types, there are only one or two studies. Additionally, this figure should only contain dietary studies, as the name suggests, yet Dr. Etminan included the Richardson occupational study for blood cancer. Consistency must be evaluated by type of cancer as risk factors vary across cancer types, and the ability of individual studies to control for these confounders can vary considerably.

Strength of Association

Strength of association is Hill's (1965) first criterion. Here again, Dr. Etminan invokes an occupational study of rubber workers, Hidajat et al. (2019), which cannot be used to demonstrate strength of association for NDMA. Dr. Etminan cites Zhu et al. (2014) and Knekt et al. (1999) as demonstrating evidence of the strength of association for colon cancer (RR=1.42; 95% CI 1.03-1.96), (RR=2.12; 95% CI 1.04-4.33), respectively. The limitations of Zhu et al. (2014) and Knekt et al. (1999) are described above. Furthermore, a RR of 1.42 would be considered "weak" and a RR of 2.12 would be considered "moderate" (WHO 2000).

Experimental Evidence

Dr. Etminan believes that the criterion of experimental evidence does not play a role in evaluating whether NDMA/NDEA are causally associated with an increased risk of cancer.

Coherence

Dr. Etminan believes that the criterion of coherence has been met because there is "coherence between basic science and epidemiological evidence." The criterion has not been met because the epidemiologic evidence does not demonstrate that NDMA or NDEA intake is causally associated with an increased risk of any type of cancer.

Expert Report of Stephen M. Lagana

While Dr. Lagana's background is in pathology, he purports to assume an epidemiologist's role by undertaking an analysis of the literature regarding the causal association between NDMA/NDEA and risk of cancer. In doing so, Dr. Lagana provides liberal interpretations of certain studies and mis-cites the literature. For instance, when referencing Al-Kindi and Oliveira (2019), Dr. Lagana makes the following statements: "What is particularly striking about this article is that the calculated risk of reporting a neoplasm as an adverse event was 70% higher for valsartan users compared to consumers of other angiotensin receptor blockers even before the NDMA contamination was announced. So although the announcement of contamination may have caused some people to make reports, and some people may have erroneously attributed their cancer to contaminated valsartan, there is no such psychosocial reason to explain 70% higher likelihood of reporting cancer in valsartan users before the contamination was public knowledge." This is not expressly stated anywhere within Al-Kindi (2019). Furthermore, not all neoplasms, which is what Al-Kindi and Oliveira describe in their report, are cancerous. Therefore, even assuming Dr. Lagana's interpretation of Al-Kindi and Oliveira (2019) is correct, his statement of "70% higher likelihood of reporting ***cancer*** in valsartan" is misleading. Finally, FAERS data alone cannot be used to establish rates of events, evaluate a change in event rates over time or compare event rates between drug products. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with drug products. Such data do not represent all known safety information for a reported drug product and should be interpreted in the context of other available information. Dr. Lagana's liberal interpretation of this data to support his causation opinions is, therefore, wholly improper.

Dr. Lagana also misapplies the Bradford Hill criteria in his evaluation of whether there is a causal association between NDMA and the risk of cancer. This is discussed in further detail, below.

Strength of Association

Dr. Lagana states that Loh et al. (2011) is a cohort study of "dietary exposure to NDMA" and that the highest exposure group was 46% more likely to develop rectal cancer than the lowest exposure group. He continues, "In medicine, a 46% increased risk is a strong association, thus fulfilling the first of Bradford Hill's criteria (strength of association)." WHO (2000) describes a relative risk of 1.46 as "weak."

Consistency

Dr. Lagana describes the studies by Zhu et al. (2014) and Knekt et al. (1999) as demonstrating consistency with Loh et al. (2011). Zhu et al. (2014) is a case-control study; Knekt et al. (1999) is a cohort study.

Loh et al. (2011) found a significantly increased risk for rectal cancer (HR=1.46; 95% CI 1.16-1.84) but did not find a significantly increased risk for colon cancer (RR=0.99; 95% CI 0.83-1.18). Zhu et al. (2014) found a significantly elevated odds ratio for rectal cancer (OR=1.61; 95% CI 1.11-2.35) but did not find significantly elevated ORs for proximal or distal colon cancer in the highest NDMA exposure group. Knekt et al. (1999) found a significantly elevated risk for colorectal cancer in the highest exposure group (RR=2.12; 95% CI 1.04-4.33), but the *p* for trend across exposure groups was not significant (p=0.47).

Thus, two studies (Loh et al 2011 and Zhu et al. 2014) do not report elevations in the HR and OR for colon cancer, respectively. Zhu et al. (2014) report a significantly elevated odds ratio for rectal cancer, but case-control studies tend to overstate relative risk (Davies et al. 1988). For an odds ratio of 1.61, the relative risk would be overestimated by at least 50% (Davies et al. 1998).

No association of NDMA intake and colon cancer were found by Loh et al. (2011) and Zhu et al. (2014). Knekt et al. (1999) note that the observed association of NDMA intake and an increased risk of colorectal cancer in their study could be due to confounding. Two studies demonstrating an association between NDMA intake and rectal cancer cannot be considered evidence of consistency, particularly when the strength of association in both studies is weak.

Specificity

Dr. Lagana chose not to address this criterion.

Temporality

Dr. Lagana relied on Hidajat et al. (2019) as evidence that the criterion of temporality was met. He states, "the median latency between exposure and disease was 15 years (meaning half took longer and half took shorter). This fulfills Bradford Hill's 4th criteria (temporality)." The 15-year lag used by Hidajat et al. (2019) was not determined from the data of the study. Hidajat et al. (2019) state, "we assumed a 15-year lag between exposure and clinical manifestation." More importantly, however, Hidajat et al. (2019) is a mortality study of rubber workers. As described previously, rubber workers are exposed to a variety of substances. Hidajat et al. (2019) therefore cannot be used to demonstrate temporality.

Biological Gradient

Dr. Lagana relies on Hidajat et al. (2019) as evidence of a biological gradient (dose response) for NDMA. The Hidajat et al. (2019) study of rubber workers cannot be used to demonstrate evidence of a biological gradient for NDMA given that rubber workers are exposed to many substances including known carcinogens.

Biological Plausibility

Dr. Lagana offers theories to explain cancer-causing mechanism(s) of NDMA. The criterion of biological mechanism is intended to assist in the determination of whether the epidemiologic data show a causal association between the agent (e.g., NDMA) and the disease outcome (e.g., cancer). The epidemiologic data don't demonstrate that NDMA or NDEA are

associated with an increased risk of cancer; thus, mechanistic theories are interesting but are no substitute for epidemiologic evidence.

Experiment

Dr. Lagana states that there is a large body of literature on NDMA related to animal experiments and thus Bradford Hill's 8th criterion is satisfied. Bradford Hill intended "experiment" to apply to human data, not animal data (Hill 1965)."

Expert Report of Dipak Panigrahy

My comments on Dr. Panigrahy's report will focus on his application of the Bradford Hill criteria to assess the evidence of causal association between NDMA and the risk of cancer. Dr. Panigrahy applied the Bradford Hill criteria to evaluations of NDMA and liver, bladder, blood, gastric, intestinal, pancreatic, esophageal, prostate, lung, and kidney cancer. He also used the Bradford Hill criteria to review data on NDEA.

NDMA

Rather than review his application of the Bradford Hill criteria to NDMA and each type of cancer, I will provide comment collectively because his application of many of the criteria are similar across the types of cancer. I will, however, provide comment where he has mentioned certain epidemiologic studies.

Throughout his evaluation on NDMA and the ten different cancers described above, Dr. Panigraphy relied heavily on the Hidajat et al. (2019) occupational study of rubber workers for the criteria of strength of association, biologic gradient (dose response), and consistency. The issue with using occupational studies of rubber workers to evaluate a causal association of NDMA exposure and the risk of cancer has been adequately described in my report and previous comments on Dr. Etminan's report.

Strength of Association

Dr. Panigrahy cites Jakszyn et al. (2011) as a study demonstrating strength of association for bladder cancer even though the hazard ratio is not significantly elevated in the NDMA high exposure group and the trend across exposure groups is not significant (p=0.49). He cites the Song et al. (2015) meta-analysis as demonstrating strength of association for stomach cancer even though the summary relative risk for neither the cohort studies nor the population-based case-control studies is significantly elevated and the summary relative risk for the hospital case-control studies had high heterogeneity. Even the overall relative risk estimate of 1.34 (includes the cohort, population-based case-control, and hospital-based case-control studies) would be considered a "weak" strength of association (WHO 2000). He cites Pottegård et al. (2018) as evidence of strength of association for colorectal cancer even though, as he acknowledges, the hazard ratio is not significantly elevated. He cites Knekt et al. (1999) as evidence of strength of association for colon cancer despite Knekt et al.'s statement that "Although the association between nitrosamine intake and colorectal cancer observed here is plausible, it cannot be excluded that it may be due to confounding." Dr. Panigrahy included the Zheng et al. (2019) as evidence of strength of association for NDMA and pancreatic cancer even though the OR for exogenous NDMA was not significantly elevated; only the OR for pancreatic cancer and exposure to plant sources of NDMA was elevated. He cites the HR of 1.13 (95% CI 0.77-1.68) from Loh et al. (2011) as evidence of strength of association for esophageal cancer despite acknowledging that the HR is not significantly elevated. He cites Keszei et al. (2013) as evidence for strength of association for NDMA intake and esophageal cancer even though only esophageal

squamous cell carcinoma (ESCC) was significantly elevated; esophageal adenocarcinoma (EAC) was not. Although acknowledging that Rogers et al. (1995) did not find a statistically significant odds ratio for esophageal cancer in the highest NDMA intake category (OR=1.86; 95% CI 0.87-3.95), he still cites the study as supporting strength of evidence for esophageal cancer. He acknowledges that Loh et al. (2011) did not find a significantly elevated hazard ratio for NDMA intake and esophageal cancer yet still cites the study as evidence of the strength of association. For strength of association for NDMA intake and prostate cancer he cites a nonsignificant HR from Loh et al. (2011) and a nonsignificant HR from Jakszyn et al. (2012). For strength of association of NDMA intake and kidney cancer Dr. Panigrahy cites animal data.

Bradford Hill (1965) in his opening remarks stated, "Our observations reveal an association between two variables, perfectly clear-cut and beyond what we would care to attribute to the play of chance. What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation? *First upon my list I would put the strength of the association*" (italics added for emphasis). Dr. Panigrahy provides an occupational study of rubber workers (Hidajat et al. 2019) exposed to a multitude of substances including known human carcinogens, dietary studies with nonsignificant associations, and animal data as evidence of strength of association. The evidence that he provides does not support strength of association for the various cancers he describes.

Consistency

Dr. Panigrahy relies heavily on animal studies in his application of the Bradford Hill criterion on consistency. In the case of blood cancer, Dr. Panigrahy describes studies in frogs and mollusks as well as mice and rats. It is clear from Hill (1965) that the criterion of consistency was intended to apply to epidemiologic studies, not animal data or animal and human data together. Dr. Panigrahy has not provided evidence of consistency across epidemiologic studies for the various type of cancer that he describes.

Specificity

With respect to the criterion of specificity, he agrees that this criterion cannot be used to support a claim of causal association.

Temporality

With respect to temporality, he claims that exposure to NDMA always precedes cancer in both the human and animal studies. The Bradford Hill criteria are intended to evaluate a causal association in humans, not animals. For some of the human studies, particularly the case-control studies, it cannot be said that exposure to NDMA preceded a cancer outcome. For example, in Zhu et al. (2014), one of the studies that Dr. Panigrahy cites as evidence of strength of association for colorectal cancer, the authors used a food frequency questionnaire (FFQ) to assess dietary intake one year prior to enrollment in the study (controls) or one year prior to colorectal cancer diagnosis (cases). In the DeStefani et al. (1996) study of lung cancer, dietary data were collected by a FFQ that estimated the diet during the five years that preceded the illness. A normal latency period for cancer is 15-20 years or longer (NIOSH 2012). A FFQ taken at the time when a person has cancer assessing dietary intakes for the previous year or the previous five years does not satisfy the criteria of temporality.

Biological Gradient (Dose Response)

For biological gradient, Dr. Panigrahy relies heavily on the occupational study of rubber workers (Hidajat et al. 2019). Hidajat et al. (2019) cannot be used for evidence of dose response

for the reasons described above. In addition to Hidajat et al. (2019), Dr. Panigrahy relies on animal data for evidence of dose response for liver cancer. Again, it is clear from Bradford Hill that the criterion of dose response is intended to apply to humans not animals. For colorectal cancer, Dr. Panigrahy relies on the studies by Knekt et al. (1999), Zhu et al. (2014), and Loh et al. (2011). The trend across NDMA exposure quartiles was not statistically significant (p=0.47) in Knekt et al (1999). Loh et al. (2011) did not examine dose response for colorectal cancer. Zhu et al. (2014), a case-control study, reported a significant trend for ORs across quintiles of NDMA intake. For evidence of dose response for esophageal cancer, Dr. Panigrahy cites Hidajat et al. (2019), Rogers et al. (1995), and Kezei et al. (2013). The trend of dose response for esophageal cancer was not significant (p=0.063) in the case-control study by Rogers et al. (1995) and the OR for the highest NDMA exposure intake was not significant (OR=1.86; 95% CI 0.87-3.95). The trend for dose response for ESCC was significant only in males in Keszei et al. (2013); it was not significant in females. The trend for EAC was not significant in males or females. Thus, the only study that could be said to demonstrate evidence of dose response is the case-control study by Zhu et al. (2014); however, Zhu et al. (2014) had significant limitations. Only 65% of cases responded to the questionnaire and only 53.3% of controls responded to the questionnaire. As indicated above, the FFQ was used to assess dietary intakes one year before enrollment (controls) or one year before diagnosis (cases), which raises significant questions as to whether temporality has been met. Dr. Panigrahy has not provided evidence that a biological gradient has been met for any of the cancers he discusses.

Plausibility

For each of the cancers that he discusses, Dr. Panigrahy makes the opening statement with respect to plausibility, "As set forth in detail in the Key Characteristics section of this report, there are 9 clear biologically plausible mechanisms for NDMA to cause cancer including ____ cancer." He does not state with certainty which mechanism is associated with any of the types of cancer he describes. Even if a mechanism could be established with certainty, a determination of a causal association of NDMA with human cancer risk cannot be made without satisfying most, if not all, the criteria that precede plausibility. Those criteria have not been satisfied.

Coherence

For each of the cancers he discusses, Dr. Panigrahy makes the following opening statement with respect to coherence, "NDMA induced cancer is consistent with the generally known facts and the biology of cancer." He then proceeds through a description of what he believes these facts and the biology of cancer are. The description is similar across each of the cancers he discusses. Like biologic plausibility, the criterion of coherence is intended to assist in determining whether the epidemiologic data demonstrate a causal association of NDMA and human cancer risk. That determination cannot be made without satisfying most, if not all, the criteria that precede plausibility, and those criteria have not been satisfied.

Experiment

Dr. Panigrahy believes the criterion of experiment as described by Bradford Hill (1965) cannot be satisfied because it would be unethical to conduct randomized control trials on human subjects.

Analogy

Dr. Panigrahy makes the following statement with respect to analogy throughout all the discussions on NDMA and the various cancers: "N-nitroso compounds, which include NDMA, are known to display extremely high carcinogenic potency. This lends support to a causal relationship between NDMA exposure and human cancer. I assigned moderate weight to this factor." Dr. Panigrahy doesn't describe the data on "N-nitroso compounds that are known to display extremely high carcinogenic potency."

NDEA

Strength of Association

Dr. Panigrahy cites the pancreatic case-control study by Zheng et al. (2019) as evidence of strength of association. Dr. Panigrahy states, "The study reported a 35% increased risk[10] for Quartile 2 that did not rise to statistical significance (OR=1.35; 95% CI: 1-1.82), 89% statistically significant increase in risk of pancreatic cancer (OR= 1.89; 95% CI: 1.41-2.53) for Quartile 3 and 128% statistically significant increase in risk of pancreatic cancer (OR= 2.28; 95% CI: 1.71-3.04)." As indicated previously, ORs can exaggerate the relative risk (Davies et al. 1998). An OR of 2.28 would translate to a relative risk less than 1.5 (Davies et al. 1988), which would be a "weak" strength of association (WHO 2000), which is contrary to Dr. Panigrahy's conclusion that Zheng et al. (2019) "strongly supports" a strength of association.

Consistency

Dr. Panigrahy states that there are "numerous animal cancer studies that show a clear association between NDEA exposure and liver, lung, gastric, blood, esophageal and kidney cancers. Zheng shows a statistically significant association between NDEA exposure and pancreatic cancer. The Zheng study together with the consistency of the association between NDEA exposure and cancer across many mammalian species including mice, rats, hamsters, guinea pigs, rabbits, dogs, swine, monkeys, snakes, fish, mollusks, cats, gerbils, prosimian bushbabies and chickens, studied by several researchers, using different study designs, over several decades is significant and gives strong support in favor of a causal association." Consistency is intended to mean multiple studies showing the same effect. Dr. Panigrahy does not present any studies other than Zheng et al. (2019) that demonstrate an association of NDEA exposure and pancreatic cancer. In fact, he presents no other epidemiologic studies of NDEA whatsoever. Bradford Hill (1965) does not indicate that consistency is intended to apply to human and animal studies, much less snakes and mollusks.

Specificity

With respect to the criterion of specificity, he indicates that this criterion cannot be used to support a claim of causal association.

Temporality

With respect to temporality, Dr. Panigrahy claims that exposure to NDEA always preceded cancer in both the human and animal studies. The Bradford Hill criteria are intended to evaluate a causal association in humans, not animals. Zheng et al. (2019) was a case-control study. Participants were asked to complete a FFQ when they were recruited. A normal latency period for cancer is 15-20 years or longer (NIOSH 2012). A FFQ taken at the time when a

[10] Dr. Panigrahy misunderstands what odds ratios (OR) are. The OR represents the odds that an outcome will occur given a particular exposure compared to the odds of the outcome occurring in the absence of exposure. It should not be used to indicate a % increase in risk.

person has cancer assessing dietary intake at the time of recruitment does not satisfy the criteria of temporality.

Biological Gradient (Dose Response)

Dr. Panigrahy cites Zheng et al. (2019) as evidence of a biological gradient. It is the only epidemiologic study examining the association of pancreatic cancer and NDEA exposure. Dr. Panigrahy also asserts that animal studies have shown a dose response of cancer with NDEA. It is clear from Bradford Hill that the criterion of dose response is intended to apply to humans, not animals.

Plausibility

A determination of a causal association of NDEA with human cancer risk cannot be made without satisfying most, if not all, the criteria that precede plausibility. Those criteria have not been satisfied.

Coherence

Like biologic plausibility, the criterion of coherence is intended to assist in determining whether the epidemiologic data demonstrate a causal association of NDEA and human cancer risk. That determination cannot be made without satisfying most, if not all, the criteria that precede plausibility, and those criteria have not been satisfied.

Experiment

Dr. Panigrahy believes the criterion of experiment as described by Hill (1965) cannot be satisfied because it would be unethical to conduct randomized control trials on human subjects.

Analogy

Dr. Panigrahy cites the National Toxicology Program (NTP) report on carcinogens as indicating that 15 N-Nitrosamines are reasonably anticipated to be human carcinogens. All these classifications are made based on animal data. None are based on human data. Thus, there is no analogy to human data. Interestingly, Zheng et al. (2019) found that NDEA was potentially associated with pancreatic cancer, but NDMA was not.

Summary of Plaintiffs' Expert Reports

Three of the plaintiffs' experts (Etminan, Lagana, and Panigrahy) have used the Bradford Hill criteria (Hill 1965) to support their positions that NDMA/NDEA are causally associated with an increased risk of cancer. Drs. Etminan and Lagana have chosen to apply the criteria without regard to specific cancer types. Causal relationship must be determined by individual cancer site as risk factors vary by cancer site and many of the studies are limited by their inability to adjust for these risk factors.

All three of the plaintiffs' experts relied on Hidajat et al.'s (2019) study of rubber workers to support various Bradford Hill criteria. As detailed in my report, rubber workers are exposed to a variety of substances, several of which are known carcinogens; Hidajat et al. (2019) had no data on smoking; and a study of the same cohort by McElvenny et al. (2018) contradicted the results of Hidajat et al. (2019). Hidajat et al. (2019) should not be used by plaintiffs' experts in their application of the Bradford Hill criteria.

Bradford Hill regarded strength of association as the most important criterion in establishing causal association. All the cohort studies cited by plaintiffs' experts reported relative risks or hazard ratios below 1.5 for various types of cancer, with one exception. Knekt et al.

(1999) reported a relative risk of 2.12 (95% CI 1.04-4.33) for colorectal cancer in the highest NDMA exposure group; however, the trend was not significant across exposure groups (p = 0.47). Furthermore, Knekt et al. (1999) themselves stated, "Although the association between nitrosamine intake and colorectal cancer observed here is plausible, it cannot be excluded that it may be due to confounding." A relative risk of >1.0-<1.5 is considered a "weak" strength of association; a relative risk of 1.5-3.0 is considered a "moderate" strength of association (WHO 2000). Three of the case control studies reported ORs > 3.0 (DeStefani et al. 1996, 1998; Goodman et al. 1992); however, as described in this report, case-control studies overestimate relative risk.

Bradford Hill's second criterion was consistency. Dr. Etminan claimed that consistency was met because there was consistency between epidemiologic studies and basic scientific studies. The criterion of consistency is intended to apply to consistency of epidemiologic studies, not between epidemiology and basic scientific studies. Dr. Lagana claimed that consistency was met because three studies found similar results but is vague about what he found consistent. Dr. Panigrahy routinely invokes Hidajat et al. (2019) as being consistent with animal studies, in some cases he includes studies on snakes, fish, and mollusks with the animal studies. In a few cases, he reports consistency between Hidajat et al. (2019) and dietary studies. Again, consistency is intended to apply to epidemiology studies; it is not intended to apply to consistency between animal and epidemiology studies.

Specificity is the third Bradford Hill criterion. All the plaintiffs' experts indicated that specificity was not met.

The fourth criterion is temporality. Dr. Etminan stated that in all the epidemiologic studies NDMA exposure preceded the outcome and specifically called out Hidajat et al. (2019). Dr. Lagana relied on Hidajat et al. (2019) exclusively as evidence of temporality. Dr. Panigrahy stated that exposure to NDMA/NDEA preceded the outcome in both animal and human studies. Again, Bradford Hill criteria are not intended to be applied to animal data, and Hidajat et al. (2019), for reasons described above, cannot be used to demonstrate temporality for NDMA. Also, as described above, case-control studies which obtained dietary data for 1-5 years preceding diagnosis should not be used to establish temporality for cancer, which may have a 15–20-year latency period between exposure and disease (NIOSH 2012).

Dr. Lagana relied exclusively on Hidajat et al. (2019) as evidence that a biological gradient (dose response) has been established. Dr. Etminan relies on Hidajat et al. (2019) but also cites some "dietary studies" although several of the "dietary studies" he cites are questionable as to dose response (e.g., the dose response in Knekt et al. 1999 is not statistically significant; Richardson et al. (2008) is an occupational study, not a dietary study; the dose-response is not significant in Rogers et al. 1995, etc.). Dr. Panigrahy relies heavily on Hidajat et al. (2019) as evidence of dose response.

Drs. Etminan, Lagana, and Panigrahy all claim there is biologic plausibility for NDMA increasing cancer risk but are not specific about the biologic mechanism. Regardless of whether a mechanism exists, however, a causal association cannot be made without evidence from the epidemiologic data, and such evidence does not exist.

Dr. Lagana does not address the criterion of coherence. Dr. Etminan believes the criterion has been met because "there is a link or coherence between basic science and epidemiologic

evidence." Dr. Panigrahy makes a similar argument. Again, a causal association cannot be made without evidence from the epidemiologic data, and such evidence does not exist.

Drs. Etminan, Lagana, and Panigrahy believe the criterion of experiment does not apply to NDMA.

Dr. Etminan believes that analogy has been demonstrated because he claims that nitrites have been shown to increase the risk of cancer. He cites the case-control study of pancreatic cancer by Coss et al. (2004) as evidence. Coss et al. (2004), however, doesn't find significantly elevated risks of pancreatic cancer from dietary nitrites. Dr. Lagana doesn't address the criterion of analogy. Dr. Panigrahy believes the criterion of analogy has been satisfied because "N-nitroso compounds, which include NDMA, are known to display extremely high carcinogenic potency," but he doesn't describe the evidence.

In summary, the arguments of Drs. Etminan, Lagana, and Panigrahy for a causal association of NDMA or NDEA with any form of cancer are totally without merit.

Use of Exhibits During Trial

I may use at trial exhibits as a summary or in support of my opinions including: (1) any of the materials, or excerpts identified in this report and attachments, including the materials considered list; (2) excerpts from scientific articles or learned treatises; (3) demonstrative models; (4) exhibits used by Plaintiffs' experts, or other witnesses; (5) any exhibit used in or identified at any deposition taken in this litigation. If further data becomes available, I will be happy to review it and consider whether to modify any portion of these opinions.

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